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EXPERIMENTAL STUDIES OF THE INTESTINAL FLORA*

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INTRODUCTION

The following experiments were carried out with the purpose of ascertaining the effect of various foods commonly used in infant feeding on the bacterial flora of the intestinal tract.

It was necessary to ascertain whether the number and variety of organisms varied in different parts of the intestinal tract. It is well recognized that but a small percentage of the bacteria occurring in the feces are viable. Bacteriologic studies of the feces, therefore, have justly been criticized on the ground that the findings give inaccurate data concerning the flora at other levels. Many workers in the field of the intestinal bacterial flora of infants have claimed that definite characteristic flora occur at certain parts of the intestinal tract. Attention has been called especially to the peculiarities of the duodenal flora.

Attention has been directed by many writers to the effect certain foods containing relative high percentages of carbohydrates or proteins have on the intestinal flora. Certain popular conceptions of the different types of intestinal disturbances in infants are based on the bacterial changes these foods are supposed to produce. If a diarrhea, for instance, occurs after a diet with a high carbohydrate content, this is called a "fermentative" condition. Under these circumstances the intestinal flora is considered to consist of organisms that act primarily on the carbohydrates. The products of this action are thought to produce the diarrhea. Similarly a disturbance associated with the feeding of a diet containing a high percentage of protein is considered to be due to "putrefaction."

It is a matter of dispute whether these intestinal disturbances are caused by primary chemical changes, or whether they are due to initial bacterial activity. As food containing a large amount of sugar is frequently associated with diarrhea in infants, studies were made to see

* Submitted for publication Nov. 7, 1916.

* From the Department of Pediatrics and Bacteriology, Johns Hopkins University.

if the condition was accompanied by changes in the bacterial flora. Attention was paid not only to whether a change took place, but also at what level the change occurred.

Studies were made to determine the effect of starvation on the bacterial flora at different levels, both after a normal diet and after a diet which caused diarrhea.

Experimental Studies. Series 1

Technic.—The experiments were carried out on puppies a few weeks of age. The animals were cared for in a private house where ample space could be given for normal activities, as it was found that the animals after being weaned did very poorly under ordinary laboratory conditions. The attempt was made to eliminate from the series all animals with intestinal parasites. The technic employed for the study of the intestinal flora was as follows: The puppies were etherized, without previous administration of a sedative. A laparotomy was then performed under antiseptic precautions. After placing presection sutures and clamping the intestinal wall at a distance of about 3 to 5 cm. on either side of the suture, the gut was punctured with a medium sized record syringe needle and 3 c.c. of sterile saline introduced. This was drawn back into the syringe and the procedure repeated three or four times in order to insure a thoroughly mixed specimen of the fecal contents. Material was removed from the duodenum at the level of the tail of the pancreas, from the ileum about 8 cm. proximal to the ileocecal valve, and from the cecum about 8 cm. distal to the ileocecal valve. A specimen of the contents of the colon was also recovered in each experiment by means of a rectal tube. The animals made excellent operative recoveries.

The bacteriologic studies were carried out as follows: Two or more smears, stained by Gram's method, were made from the specimens recovered. Examination of these preparations gave helpful information as regards the actual presence of organisms, a general impression of the relative number present and a picture of the various types from a morphologic point of view. Four plates were made from each specimen on the following mediums: plain agar, dextrose litmus agar, 2 per cent. acid dextrose agar, and whey agar. Dilutions were not usually made from the duodenal and ileal specimens. In a few instances in which smears showed no organisms, or very few, cultures were made, after incubation of the specimen. Special studies for acidophilic organisms were carried out by making three transfers to 3 per cent. acid broth, after intervals of two days, and finally plating on 2 per cent. acid whey agar. As spore-bearing forms are easily inhibited by *Bacillus coli,* one specimen of the intestinal content, in each instance, was heated for fifteen minutes at 80 C., and then plated on the usual mediums.

Group 1. *Controls.*—Observations were first made on the intestinal contents of five puppies, which were used as controls. The diet consisted exclusively of whole milk (pasteurized), fed over a period of seven to ten days. The following experiments show the characteristic results.

These experiments show that the bacterial flora of young puppies fed on cow's milk is essentially the same as that of infants on a similar diet. The acidophilic bacilli found in small numbers in stools of infants fed on cow's milk were not noted in these studies. All the various organisms observed in the colon (the findings of the colon were identical with those of the cecum and have not been recorded) were found at the other levels. Fewer organisms, especially after

ingestion of small amounts of food followed by periods of starvation, were found in the duodenum than elsewhere. There seems to be a gradual increase in the number of organisms from the duodenum to the cecum. Although *Bacillus coli* is the predominating type, the variety of organisms present is so great and their relative number so variable that one cannot speak of a characteristic flora at any level.

TABLE 1.—EXPERIMENT 6. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
1 mo.	Whole milk; 2 ounces at last feeding	4 hrs.	Smear: Organisms, +++* G— bacilli, ++ G+ cocci, + Large G+ bacilli and yeasts Culture: B. coli and B. lactis-aerogenes, ++ Strep. lact., + Spore bearing forms, rare Acidophilic bacilli, 0	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, + G+ cocci, — Spirillae, + Culture: B. coli, ++ Acidophilic bacilli, 0	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, ++ G+ cocci, rare Spirillae, + Culture: B. coli, ++ B. lactis-aerogenes, + Spore bearing forms, + Acidophilic bacilli, 0

* In this and the following tables +++ = very numerous, ++ = many, + = few, G = gram.

TABLE 2.—EXPERIMENT 9. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
1½ mos.	Whole milk; 1 ounce at last feeding	5 hrs.	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, ++ G+ cocci, rare Culture: B. coli, + Strep. lact., rare Acidophilic bacilli, 0	Smear: Organisms, +++ G+ bacilli, ++ G+ cocci, + Culture: B. coli, ++ Spore bearing forms Acidophilic bacilli, 0	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, + Spirillae, + G+ cocci, + Culture: B. coli, ++ Spore bearing forms, + Acidophilic bacilli, 0

TABLE 3.—EXPERIMENT 15. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2½ mos.	Cow's milk for past 11 days; 2 ounces at last feeding	8 hrs.	Smear: Organisms, + G— bacilli, rare Culture: B. coli, rare Strep. lact. No acidophilic bacilli	Smear: Organisms, ++ G— bacilli, + G+ bacilli, rare G+ cocci, rare Culture: B. coli, ++ Yeasts, rare Strep. lact., rare No acidophilic bacilli	Smear: Organisms, +++ G+ bacilli, rare G— bacilli, rare G+ cocci in clusters, + Culture: B. coli, ++ Strep. lact., rare Yeasts, rare Spore bearing forms No acidophilic bacilli

GROUP 2. *Experiments with High Sugar Diets.*—Eleven puppies were fed pasteurized cow's milk, with additional lactose, four with additional sucrose. With rare exceptions the animals took this modification well. Typical experiments of this group are given.

TABLE 4.—EXPERIMENT 11. LACTOSE FEEDING

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	Milk +, 10% extra lactose for 9 days; amount last feeding, 2 ounces	2 hrs.	Smear: Organisms, + G— bacilli, + G+ cocci, rare G+ bacilli, rare Culture: B. coli, + B. lact.-aerog., + Spore bearing forms, + Strep. lact., + Acidophilic bacilli, 0	Smear: Organisms, +++ G+ bacilli, + G— bacilli, + G+ cocci, + Culture: B. coli, ++ Strep. lact., rare Spore bearing forms, rare Acidophilic bacilli, 0	Smear: Organisms, +++ (poor definition) G— bacilli with + granular appearance G+ bacilli, + G+ cocci, rare Culture: B. coli, ++ Strep. lact., + Spore bearing forms, + No acidophilic bacilli

TABLE 5.—EXPERIMENT 22. LACTOSE. FASTING AFTER DIARRHEA. STARVATION PERIOD 18 HOURS

Age	Diet	Period	Duodenum	Ileum	Cecum
1 mo.	Whole milk, 10% extra lactose; diarrhea, ++	4 days; 18 hrs. fasting	Smear: G+ bacilli, rare Organisms, rare (most fields no organisms) Culture: Strep. lact., rare Spore bearing forms All isolated colonies 1-10 on a plate Acidophilic B., 0	Smear: G— bacilli, rare G+ bacilli, rare Most fields without organisms (rarely 1 to 5) Culture: Spore bearing forms B. coli, + B. lact. aerogenes (isolated colonies of above, 10-20 on a plate) Acidophilic B., 0	Smear: Organisms, +++ G— bacilli, + G+ bacilli, + G+ cocci, + Culture: B. coli, ++ Spore bearing forms, ++ Strep. lact., ++ Acidophilic B., 0

TABLE 6.—EXPERIMENT 19. LACTOSE FEEDING (STARVATION)

Age	Diet	Starvation	Duodenum	Ileum	Cecum
2 mos.	Whole milk + 10% lactose; fed for past 10 days without diarrhea; amount last feeding, 2 ounces	20 hrs.	Smear: Organisms, rare* G— bacilli, rare Cultures: Strep. lact. B. coli Spore bearing forms (isolated colonies of each) Acidophilic bacilli, 0	Smear: Organisms, rare, few† G— bacilli B+ bacilli G+ diplococcus Cultures: B. coli Strep. lact. Yeasts (few colonies of each) Acidophilic bacilli, 0	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli (few) Spirillae G+ cocci Cultures: B. coli and L. aerogenes, + Strep. lact. (many colonies of each) Acidophilic B., 0

* Rare; many fields without any organisms.
† Few, 2 to 5 in a field.

TABLE 7.—EXPERIMENT 25. LACTOSE WITH DIARRHEA (STARVATION)

Age	Diet	Fasting	Duodenum	Ileum	Cecum
7 wks.	Whole milk + 10% extra lactose for past 10 days; diarrhea 36 hrs. before operation (not at time of operation); 6 ounces at last feeding	20 hrs.	Smear: Organisms, + G— bacilli G+ cocci Culture: B. coli, + Strep. lact., + (scattered colonies of each) No acidophilic bacilli Presence of spore bearing forms Mesentericus; large spreading colonies	Smear: Organisms, ++ G— bacilli, + G+ bacilli, + Culture: B. coli, + Strep. lact., + Spore bearers, + No acidophilic bacilli Presence of spore bearing forms Profuse growth; mesentericus and cereus	Smear: Organisms, +++ G— bacilli, + G+ bacilli, + G+ cocci, + Culture: Strep. lact., + B. coli, ++ No acidophilic bacilli Presence of spore bearing forms Colonies of mesentericus subtilis (pseudotetanus)

TABLE 8.—EXPERIMENT 14. CANE SUGAR

Age	Diet	Starvation Period	Duodenum	Ileum	Cecum
2½ mos.	Whole milk with cane sugar to 13%	7 hrs.	Smear: Organisms, + G. bacilli G+ bacilli G+ cocci, all rare Culture: B. coli Acidophilic organisms, 0 Spore bearing forms, +	Smear: Organisms, + G— bacilli, + G+ bacilli, + Culture: B. coli, rare Acidophilic, 0 (desquamated epithelial cells)	Smear: Organisms, +++ G— bacilli, ++ G+ cocci, rare Culture: B. coli, ++ Strep. lact. Strep. (fecalis) Acidophilic bacilli, 0

The studies of the bacterial flora of puppies fed diets containing from 10 to 15 per cent. of lactose or sucrose show that the same organisms are present as under normal dietary conditions. Even with diets with a very high carbohydrate content, no acidophilic organisms are present at any level. As in the previous group of experiments, there is a close agreement between the microscopic and cultural findings. Examination of the intestinal contents of puppies with a profuse diarrhea after a high carbohydrate diet show no essential variation from the findings previously noted. The same diminution in the number of organisms after starvation is noted in this group of experiments as in the foregoing.

In addition to the effect of dietary changes on the intestinal bacterial flora, the results of the foregoing experiments show that after periods of starvation of from eight to twenty hours, the number of organisms in the small intestine is greatly reduced. This diminution is more marked in the duodenum, but is evident as far down as the cecum. The reduction in the number of organisms seems to be in pro-

portion to the length of the fasting period and the amount of food taken before the starvation, the longer periods of fasting and the previous ingestion of little food giving the greatest reduction in organisms. Although many of the plates and smears from specimens under those conditions showed no organisms, in every experiment bacteria were demonstrated at each level. No changes in types of organisms were shown to exist after periods of fasting.

GROUP 3. *Protein Milk Diet.*—Some difficulty was experienced in feeding the puppies protein milk. In but one instance did the animal take this well.

TABLE 9.—EXPERIMENT 10 (PROTEIN MILK)

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	Protein milk; 2 ounces last feeding partially vomited	2 hrs.	Smear: Organisms, ++ G— bacilli, + G+ bacilli G+ cocci Culture: B. coli and B. lact. aerogenes, ++ Special test for spore bearing forms, + Acidophilic, 0	Smear: Organisms, +++ G— bacilli, ++ G+ cocci, + G+ bacilli Culture: B. coli, ++ Spore bearing forms, +	Smear: Organisms, +++ G— bacilli and spirillae, ++ G+ bacilli and cocci, ++ Culture: B. coli, ++ Spore bearing forms, +

TABLE 10.—EXPERIMENT 24. PRESENCE OF SPORE BEARING FORMS

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	15% lactose without diarrhea; period feeding, 1 week; 4 ounces last feeding	20 hrs.	No growth	Many colonies of spore bearing forms mesentericus cereus subtilis yeasts	Few colonies of spore bearing forms mesentericus

The bacterial intestinal flora of a dog fed on protein milk is essentially the same as was found under normal dietary conditions. Although the spore-bearing forms are more numerous, they do not become the predominating type. It is seen that spore-bearing organisms occur at all levels in relatively large numbers, in animals fed on a diet high either in carbohydrates or in proteins.

EXPERIMENTAL STUDIES. SERIES 2

A second series of studies was made on infants. A duodenal catheter was passed, as has been described by Hess,[1] and duodenal con-

1. Hess, A. F.: The Use of a Simple Duodenal Catheter in the Diagnosis and Treatment of Certain Cases of Vomiting in Infants, AM. JOUR. DIS. CHILD., 1912, **3**, 133.

tents were then aspirated. The specimens were studied as in the foregoing series of experiments. Typical reports of this series are given below. Ten cases were studied.

TABLE 11.—STUDY 2

Subject	Diet	Hours after Feeding	Results
Baby B., aged 5 mos.; normal	Whole milk	2	1. 5 c.c. of yellow turbid material with soft whitish curds; recovered 2. Smear: Organisms, +++ (not unlike fecal specimen); gram ++ cocci; gram — bacilli 3. Cultures: Staphylococci, +; Streptococcus lacticus, +; B. coli and Lactis aerogenes, ++; yeasts and spore bearing forms, rare

TABLE 12.—STUDY 4

Subject	Diet	Hours after Feeding	Results
Normal, 4 months' infant	Whole milk modification	2	1. ¾ c.c. rather viscid, yellow, turbid material 2. Smear: Organisms, ++; gram— bacilli, +; gram+ cocci, + 3. Culture: B. coli and B. lactis-aerogenes, +

TABLE 13.—STUDY 5, BY MODIFICATION OF FORMER TECHNIC*

Subject	Diet	Hours after Feeding	Results
Normal, 5 months' infant	Breast milk, with supplementary feedings of cow's milk	5	1. Small amount (0.5 c.c.) slightly turbid fluid 2. Smear: No organisms noted 3. Cultures: B. coli, rare; B. lactis-aerogenes, +; Streptococcus lacticus, +

* In this instance, 10 c.c. of normal saline was introduced into the duodenum before aspiration.

The observations made on infants by means of a duodenal catheter show that not only a large number of organisms may be present in the duodenum, but that these may be very similar to the organisms occurring in the feces. Cocci of various types are more numerous in the duodenum than are commonly found in the fecal specimens. The predominating organisms at this level when large numbers of forms are present is a gram-negative bacillus; these are *Bacillus coli* and *Bacillus lactis-aerogenes*. It will be noted that the coccus forms referred to above are similar to those present normally in the mouth.

DISCUSSION

Localization of Flora.—From the experiments recorded it is seen that the flora of the intestinal tract at various levels is essentially the same, as determined by our present bacteriologic methods. Although the organisms recovered from the feces showed poorer definition and staining properties than those recovered from other levels, the same types of organisms were noted microscopically, and culturally they were found to be nearly the same in all regions. It seems, therefore, that the study of fecal specimens gives quite a true, adequate picture of the flora that may occur at any of the different levels of the entire intestinal tract. It is of special interest to find that so many forms may be present in the duodenum of the normal infant, and that these may be very similar to forms found at lower levels. It has not infrequently been stated that such a condition was in all probability associated with gastro-intestinal disorders. Tobler[2] asserts that the digestive processes of the duodenum are unaccompanied by the activities of bacteria. The method of recovering the specimens with the duodenal catheter is not entirely satisfactory, as it is impossible to avoid completely contaminations from the mouth and upper alimentary tract. In regard to the relative number of organisms present at the various levels, the experiments show that during the early periods of digestion there is no recognizable variation. Where so many organisms are present, we feel that we have no satisfactory method of determining with sufficient accuracy an estimate of the absolute number.

Effect of Diet on the Flora.—Moro[3] and others have called attention to changes in the bacterial flora of infant stools after various diets. An acidophilic, gram-positive group of bacilli was considered characteristic of infants fed on breast milk. The feces of children fed on cow's milk was found to contain few of these organisms and numerous *B. coli, cocci* and proteolytic forms. Wollstein[4] investigated stools of infants fed on high protein and carbohydrate diets. On carbohydrate high diet, "cocci, colon bacilli, acidophilus and bifidus bacilli were most numerous." "During the periods of high protein content in the food, *B. mesentericus* gained the ascendancy, *B. aerogenes-capsulatus* sometimes persisted, and the colon bacilli were increased in numbers. But the acidophilus and bifidus did not entirely disappear." From the writings of these authors it is to be assumed that in their belief certain quantitative changes result from varying the food. Herter and

2. Tobler, L., and Bessau, G.: Krankheiten durch abnormen Ablauf der Ernährungsvorgänge und des Stoffwechsels, 1914.

3. Moro, E.: Jahrb. f. Kinderh., 1900, **52**, 38.

4. Holt, L. E.; Brown, A.; Wollstein, M., and Courtney, A. M.: The Influence of High Protein Feeding on the General Metabolism, on the Intestinal Flora and on the Body Temperature of Infants, Am. Jour. Dis. Child., 1912, **4**, 265.

Kendall[5] fed monkeys and cats high protein diet and assert that a proteolytic flora was obtained.

Few experimental studies of the intestinal bacteriology of animals, after changes in diets, have been made. Rettger and Horton[6] showed that when rats were fed on a diet containing a single protein the intestinal flora became simpler. The normal flora was replaced by the acidophilic group of organisms. The authors consider that the change was "independent of the pure proteins, but bore a definite relation to the protein-free milk which formed a part of the pure protein diet." From a more recent series of experiments, Rettger[7] concludes that the intestinal flora of white rats and the domestic fowl undergoes "profound alterations" when fed on a milk diet. These changes consist in the establishment of a flora consisting of *Bacillus acidophilus* or *Bacillus bifidus,* or both of these organisms may predominate. From a further series of experiments carried out on rats fed various carbohydrates, Rettger[8] concludes that lactose in itself will cause the changes above mentioned.

Of special interest were the findings in the experiments as presented by me after feeding cow's milk containing relative high percentages of additional sugars. The flora was not only unchanged in the colon, but all the levels examined showed essentially the same organisms as after diets of unmodified cow's milk. An acidophilic flora, as noted by Rettger, in the sense of a predominating gram-positive bacillus, showing cultural characteristics of *Bacillus bifidus* and *Bacillus acidophilus,* or both of these organisms, was never obtained, either after lactose or sucrose feedings. It is possible that the difference in the species of the animals utilized for experimentation may in part explain these contradictory results. The cultural methods employed to isolate the acidophilic organisms may, indeed, have failed to show the presence of rare bacilli of this type. That they never were in predominating numbers is shown conclusively by the microscopic findings, as a smear made up chiefly of gram-positive bacilli was never encountered.

It is very difficult to say whether the diarrhea elicited by the high sugar feedings in these experiments is similar to that occurring in infants under similar conditions. The animals, in many instances, became inactive, would not play and took their feedings poorly. The

5. Herter, C. A., and Kendall, A. I.: Jour. Biol. Chem., 1908-1909, **5,** 293.
6. Rettger, L. F., and Horton, G. D.: Centralbl. f. Bakteriol., Part 1, Orig., 1914, **73,** 362.
7. Rettger, L. F.: Jour. Exper. Med., 1915, **21,** 365.
8. Rettger, L. F.: Footnotes 6 and 7.

diarrhea was easily controlled by withdrawing the sugar from the diet. The younger puppies developed diarrhea much more quickly than older ones.

The experiments with protein milk are too few to allow definite conclusions. Nevertheless, it seems significant that essentially the same types of organisms may be present in the intestinal tract on this diet as on unmodified cow's milk. It is possible that the organisms normally present under dietary conditions may change their function and act on proteins instead of carbohydrates. The reason for the beneficial effect of protein milk must still be considered as a matter of conjecture.

From those studies it seems probable that protein milk induces no marked alteration in the bacterial flora, and that, therefore, the changes produced in digestion are primarily chemical rather than bacteriologic. The fact that spore-bearing forms were found at all levels examined deserves mention. It has formerly been thought that these organisms sporulated primarily in the colon and there produced toxic compounds which caused certain digestive disturbances. In puppies, it is clear that the spore-bearing forms may occur in large numbers at upper levels of the intestinal tract without causing any unfavorable symptoms. The same statement is undoubtedly true for infants, as foods such as protein milk are known to contain large numbers of these forms, and it has been shown by Ford and Knox[9] that the ingestion of these organisms may cause no clinical symptoms.

In relation to the experiments on the effects of starvation presented in this paper, reference should also be made to the work of Cushing and Livingood.[10] These authors made observations on the number of intestinal organisms in dogs after a twenty-four-hour fast. A laparotomy was performed on an adult dog previously fed on a milk diet and starved for twenty-four hours. Specimens were then taken from ten different levels, after incision of the intestine. The specimens consisted of single platinum loopfuls of intestinal contents. Smears and cultures were made. No mention is made either of the mediums used or the method employed for counting the organisms. It should be stated that a single loopful of intestinal contents may vary so much in consistency and in number of bacteria present that estimations of the number and kind of organisms by this method are of very relative value. From their experiments the authors conclude that a relative amicrobism of the small intestine results after a period of twenty-four hours' starvation. Study of the distal loops of two patients with permanent fistula of the jejunum showed a sterile condition. These and further

9. Knox, J. H. M., Jr., and Ford, W. W.: Bull. Johns Hopkins Hosp., 1915, **26,** 27.

10. Cushing and Livingood, L. E.: Contributions to the Science of Medicine, by Pupils of Welch, 1900, p. 543.

observations on a series of twenty-seven dogs and eight rabbits confirmed the conclusion given above. These last experiments were undertaken from a surgical rather than from a strict bacteriologic point of view. Careful dietary precautions were not taken. These authors also conclude from their experimental studies that one is not justified in speaking of a local flora at particular levels.

Effects of Starvation.—The examinations of the intestinal contents after periods of starvation show definite changes in the number of organisms. In many instances smears showed rare forms, and many times the plates showed but isolated colonies, in contrast to the profuse growth found normally. Changes in the kinds of organisms persisting after periods of starvation were not noted. The greatest diminution was observed in the duodenum. In some instances, however, only rare organisms were present in the contents of the ileum. The contrast between the paucity of organisms at this level and the large number present in the cecum was striking. Although the number of organisms is, to a great extent, dependent on the food residue present, absolutely sterile specimens, even after the food residue was undoubtedly absent, were never obtained. In other words, the condition produced by starvation is one of relative amicrobism.

CONCLUSIONS

From the experimental studies on the intestinal flora of puppies, the following conclusions can be drawn:

1. In puppies the types of organisms occurring at the duodenum, ileum, cecum and rectum are in all instances similar. One cannot speak of a characteristic local flora occurring in these regions.

2. Feedings to puppies of cow's milk mixtures with high percentage of sucrose or lactose does not cause characteristic changes in the intestinal flora at any level, even when a diarrhea is produced.

3. Starvation of twenty-four hours renders a relative amicrobism of the small intestine.

THE HEMATOLOGY OF INFECTIOUS DIARRHEA *

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NEW ORLEANS

In reviewing literature relative to this subject, the writer has found a total absence of any authentic conclusions regarding the blood in infectious diarrhea. Starr,[1] Whipham[2] and Keating[3] make no mention of the blood whatsoever. Taylor and Wells,[4] Ashby and Wright,[5] Carmichael[6] and Oppenheim[7] also failed to mention this important point. The textbooks of Donkin,[8] Smith,[9] Carr[10] and Cotton[11] have left unsaid all matters pertaining to this subject. Even the most recent works on pediatrics, by such authorities as Koplik,[12] Hutchinson,[13] Chapin and Pisek,[14] Rachford,[15] Cautley,[16] Fischer,[17] McCaw,[18] Rotch,[19] Still,[20] Holt,[21] Garrod, Batten, Thursfield[22] and Morse,[23] have all left this important topic untouched. In addition, a careful survey of the works of different authorities who have made hematology a special study in the majority failed to record even a single fact on this subject. Buchanan,[24] Ward,[25] Schleip,[26] Pappenheim[27] and Naegeli[28]

* Submitted for publication July 10, 1916.
* From the Boston Floating Hospital, Clinical Pathologist, August, 1914.

1. Starr: Diseases of Digestive Organs.
2. Whipham: Medical Diseases of Children.
3. Keating: Encyclopedia Diseases of Children.
4. Taylor and Wells: Diseases of Children.
5. Ashby and Wright: The Diseases of Children.
6. Carmichael: Diseases of Children.
7. Oppenheim: The Medical Diseases of Childhood.
8. Donkin: Diseases of Childhood.
9. Smith: Eustace, Diseases of Children.
10. Carr: The Practice of Pediatrics.
11. Cotton: Diseases of Infancy and Childhood.
12. Koplik: Diseases of Infancy and Childhood.
13. Hutchinson: Lectures on Diseases of Children.
14. Chapin and Pisek: Diseases of Infants and Children.
15. Rachford: Diseases of Children.
16. Cautley: Diseases of Children.
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18. McCaw: Diseases of Children.
19. Rotch: Pediatrics of Children.
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21. Holt: Diseases of Infancy and Childhood.
22. Garrod, Batten and Thursfield: Diseases of Children.
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25. Ward: Clinical Haematology.
26. Schleip: Technik der Blutuntersuchung.
27. Pappenheim: Atlas der menschlichen Blutzellen.
28. Naegeli: Blutkrankheiten und Blutdiagnostic.

have ignored this question in its entirety. Gulland and Goodall[29] say: "In severe cases there may be high counts from concentrations of blood. The casual conditions may cause alteration in the number or proportion of the white cells. In chronic cases there may be severe anemia." Even in the volumes of Pfaundler and Schlossmann[30] there is the failure to record any of these facts.

METHOD OF WORK

The month of August proved ideal in every respect, for there were variations in temperature, and all types of infectious diarrhea were portrayed, and a sufficient number to justify conclusions under the different lines of research. For convenience and also for thoroughness it was thought preferable to divide the infectious diarrheas into three groups: Group 1 to contain the cases in which the etiologic factor was the *Bacillus dysenteriae* (number of cases, sixteen); Group 2, the causative factor being the *B. welchii* (*B. aerogenes-capsulatus*) (number of cases, five), and Group 3, containing the cases with a mixed infection (number of cases, four). In all, a total of twenty-five cases were studied and watched in a detailed manner. The organisms found under the third group included *B. welchii, B. paratyphosus, B. typhosus* and streptococci. Indeed, I am glad I made these studies, because there were several important facts made out which would otherwise have been omitted.

Each morning the bacteriologist gave me a list of new cases, namely, those which were suggestive from the clinical manifestations alone. I then, on the same day, began the investigation from the hematologic standpoint. Every other day a total leukocyte count and a differential were made on the cases while in the acute stage. During the convalescent period the blood was examined not less frequently than every fourth day. In this way I studied the case from the admission and followed each one until the bacteriologic evidences for our work became negative for three successive examinations. During the period of research there were over fifty cases followed, and I have chosen twenty-five of this number, because a great many of the remaining cases proved to be other than infectious diarrhea, although clinically a number of them were thought to come within this group. The number of blood pictures per case was not less than five and not more than ten. Every day a visit in person to the individual patients was made and notations were recorded. One day out of each week the work for the previous six days was recapitulated, and if it was felt that more time was needed, the writer took an additional half day. It is hoped that

29. Gulland and Goodall: The Blood.
30. Pfaundler and Schlossman: Atlas, Diseases of Children.

the facts obtained along this line will be the stimulus for additional work, for indeed the blood manifestations of dysentery have in the past received little attention.

CLASSIFICATION

After a careful survey of the cases in question I have endeavored to classify them from a bacteriologic point of view,[31] this referring only to those which have been seen in person:

Infectious diarrhea

I. Toxic

1. Flexner
   a. Severe
   b. Moderate
   c. Mild

II. Nontoxic

2. Welchii
   a. Severe
   b. Moderate
   c. Mild

3. Mixed
   a. Severe
   b. Moderate
   c. Mild

In the severe form of the toxic type there are marked prostration, coma, great loss in weight, ruby lips, temperature of 103 persisting, dejections ten to twenty-five daily, on the one hand, or two to four, on the other, and inability to retain by mouth any food whatever.

In the moderate form of this type the symptoms given above are slightly less severe, with a temperature of not over 103, of a remitting character. Only a few dejections in this type are a rare occurrence.

In the mild form of the toxic type there is no coma, the prostration is slight, and the weight remains about uniform; there are no apparent neurologic symptoms, no perceptible loss of interest in the surroundings, and the temperature rarely reaches 101.

In the severe form of each of the two divisions of the nontoxic type the symptoms resemble those of the severe cases in the toxic group in every respect except that the coma is not as a rule so well marked and prostration does not seem to be at all proportional to the temperature and infection. The amount of fever is generally higher, particularly in the mixed infection in which the *B. welchii* is one of the organisms.

The moderate cases of these two divisions of the nontoxic group

31. From a bacteriologic standpoint as exhibited, August, 1914.

differ from the severe cases only in the lower temperature, with slight prostration, and the absence of nervous symptoms.

The mild cases of the nontoxic group manifest some peculiarities. The child appears to be slightly ill, but is interested in the surroundings, and if old enough will talk, sit up in bed and do many things appertaining to its age. Diarrhea is a constant symptom, though the loss in weight is not so great as the number of dejections would lead one to expect. Bacterial manifestations are present and one finds them in almost every examination of the stool. The patients of this group have practically no abnormalities with respect to temperature, pulse or respiration; in other words, if it were not for the diarrhea you could hardly consider the children ill, yet this condition may be the forerunner of the other two types of the disease.

TABLE 1.—THE CHARACTER OF THE DISEASE AND THE RESULT IN TWENTY-FIVE CASES OF INFECTIOUS DIARRHEA

Character	Severity	Case Number *	Recovered	Died
Toxic	Severe	1 D., 3 D., 4 D., 10 D., 16 D.	0	5
	Moderate	11 R., 14 R., 2 D., 5 R., 6 D., 7 R., 8 D.	4	3
	Mild	9 R., 12 R., 13 R., 15 R.	4	0
			— 8	— 8
Nontoxic	Severe	20 D., 21 D.	0	2
	Moderate	22 R., 19 R.	2	0
	Mild	25 D., 17 R., 18 D., 23 R., 24 R.	3	2
			— 5	— 4
			13	12

* In this column D. signifies that the patient died, R. that he recovered.

TEMPERATURE

The temperature curve in infectious diarrhea is indeed variable. The first week of illness the temperature ascends gradually, reaching as a rule the maximum from the fifth to the seventh day, although occasionally the maximum will not be reached before the beginning of the second week, with a morning remission and an evening rise during the entire fever period.

In the second week of illness the maximum temperature reached is usually from 1 to 1.5 degrees less than that of the first week.

In the third week of illness the temperature rarely exceeds 100, and most often reaches a maximum in the neighborhood of 99 and a fraction.

In the fourth week of illness the patient is generally free from fever; occasionally a slight rise to a point not exceeding 99.5 may be recorded for one day. This is due to some indiscretion and is not to be considered a part of the real curve.

The maximum temperature over 103 means the prophecy of death. Other cases in which we have an initial temperature over 105, and this followed by a fall of from 2 to 3 degrees, for the most part terminate fatally anyway. In trying to determine whether there was any direct

TABLE 2.—Duration of Fever and Percentage of Deaths in Twenty-Five Cases of Infectious Diarrhea

Number Cases	Number Days with Fever	Per Cent. Cases	Per Cent. Died
1	20	4	0
1	19	4	0
1	17	4	0
1	15	4	0
4	14	16	8
2	13	8	0
1	12	4	4
2	11	8	8
1	10	4	0
1	9	4	4
1	8	4	0
4	6	16	16
1	5	4	0
1	4	4	4
1	3	4	0
1	2	4	4
1	1	4	4

TABLE 3.—Duration of Fever Summarized in Five-Day Periods *

Number Cases	Number Days with Fever	Per Cent. Cases	Per Cent. Died
1	20	4	0
3	15	12	0
10	10	40	5
7	5	28	4
4	1	16	8

* The patients averaged ten days of fever while in the hospital.

relation between the temperature and the pulse, as contrasted in typhoid fever, the following are the results obtained:

In Flexner bacillus diarrhea, as an illustration of the pulse and temperature relation, a child of 10 months showed a temperature of 104.5 and a pulse of 120. If the pulse is taken when the child is crying,

TABLE 4.—Percentage of Period Spent in Hospital

Number Cases	Per Cent. Time in Hospital
9	100
2	90
2	80
1	70
5	60
2	50
2	40
0	30
1	20
1	10

TABLE 5.—Summary of Percentage of Period Spent in Hospital

Number Cases	Per Cent. Time in Hospital	Number Died
14	70	9
7	50	3
2	30	0
2	10	0

TABLE 6.—Range of Temperature

Number Cases	Temperature	Per Cent. Total Number	Per Cent. Died
1	106+	4	4
2	105+	8	8
4	104+	16	16
2	103+	8	4
6	102+	24	12
7	101+	28	0
3	100+	12	4

TABLE 7.—Summary of Range of Temperature

Number Cases	Temperature	Per Cent. Total Number	Per Cent. Died
7	104+	28	28
8	102+	32	16
10	100+	40	4

TABLE 8.—Duration of Illness

Prior to Admission		After Admission	
Cases	Days	Cases	Days
Group 1		Group 1	
1	1	2	2
1	2½	2	2
4	3	1	7
1	4	1	11
1	6	4	13
3	7	3	14
1	8	1	16
1	13	1	20
3	14	1	21
		1	30
Group 2		Group 2	
2	3	1	6
1	7	1	10
2	14	1	11
		1	12
		1	21
Group 3		Group 3	
1	7	1	10
1	10	1	20
1	14	2	21
1	21		
Total		Total	
1	1	2	2
1	2½	2	2
6	3	1	6
1	4	1	7
1	6	2	10
5	7	2	11
1	8	1	12
1	10	4	13
1	13	3	14
6	14	1	16
1	21	2	20
		4	21
		1	30

and this is the case in the majority of instances, of course the rate will be much greater; but, on the other hand, if it is taken when the child is at rest, as a rule a high temperature and a low pulse will be obtained, very similar to the condition in typhoid.

In the second or Welch's bacillus group the results obtained vary markedly from those of the former. As an illustration, a child of

TABLE 9.—TOTAL DURATION OF ILLNESS ARRANGED BY GROUPS

Case	Duration, Days	Case	Duration, Days
Group 1		Group 2	
1	1	1	13
2	14	1	18
2	16	1	20
1	17	1	26
1	18	1	45
2	20	Group 3	
1	21	1	17
2	23	1	30
1	26	1	35
1	29	1	42
1	44		

TABLE 10.—TOTAL DURATION OF ILLNESS *

Case	Duration, Days	Case	Duration, Days
1	11	2	26
1	13	1	29
2	14	1	30
2	16	1	35
2	17	1	42
2	18	1	44
3	20	1	45
1	21		
2	23	Average	23

* Case 5 has been omitted.

7 months showed a temperature of 100 and a pulse of 150. This typifies a peculiar combination, namely, a rather low temperature and a greatly accelerated pulse.

The cases under the group of mixed infection simulate those classified under the previous one, with the exception that the pulse is more greatly accelerated, particularly if the mixed infection contains both the *B. welchii* and streptococci.

Fever is one of the symptoms on which a degree of prognostication can be based. The limits were from 100 to 106 and a fraction. All patients who had a temperature above 104 died, and a few of those whose temperature reached but a fraction above 102 succumbed.

Of those who died, 77 per cent. succumbed in less than twenty days, and the remaining 23 per cent. died between the twenty-first and twenty-sixth days. Of those who recovered, 27 per cent. were sick under twenty days, 28 per cent. between twenty-one and thirty days, 18 per cent. between thirty and forty days and 28 per cent. between forty and fifty days.

TYPICAL CASES

CASE 13 (Group 1).—W. D. was the youngest of three children, having two sisters, aged 3 and 4 years, respectively. His father was 26 and his mother 23 years old, and both give a history of good health. There had been no known exposure to tuberculosis or to infectious diseases and no history of syphilis. The child was born at full term in normal delivery and was not ill until February, when he had bronchitis for three weeks. He was breast fed for ten months and after that time received various modifications of condensed milk with crackers and bread added to the diet.

TABLE 11.—BLOOD FINDING IN THE CASE OF W. D.

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Türck's Cells
8/ 2/14	8,600	7	19	68	1	5
8/ 4/14	12,100	9	36	49	5	1
8/ 8/14*	9,400	4	32	60	..	4
8/11/14	14,800	6	26	60	2	0
8/17/14	10,600					
8/20/14	12,800	8	60	32		
8/22/14	10,400	10	36	48		
8/25/14	12,400	2	56	36	6	
8/29/14	16,600	2	42	56		
8/30/14	15,800	4	44	52		

* Entered on the sixteenth day of illness, convalescent from Aug. 8, 1914, on.

He had been ill for two weeks at the time of admission, suffering with vomiting and diarrhea, the vomiting immediately following the intake of food. The diarrhea consisted of fifteen movements in twenty-four hours, green in color, watery in consistency, foul in odor, and containing blood and mucus. He had had fever one day, seemed somewhat prostrated and slept poorly.

Physical examination showed nutrition and development good. The cheeks were somewhat flushed and the general appearance indicated that the child was ill. The anterior fontanel was open, measuring 1.5 by 1.5 cm. There was a slight rosary, but enlargement of the epiphyses and rigidity and retraction of neck were negative. The pupils and the eyes in general, the tongue and the mouth seemed normal. He had four teeth above and two below. There were no enlarged glands and the drums of the ears were not pathologic. The heart was normal for a person of the patient's age. The left border of dulness was

4.5 cm. to the left of the midsternal line, and 0.5 cm. inside the nipple line; the right border was 2.5 cm. to the right of the midsternal line. The sounds were regular and no murmurs were heard. The lungs showed no pathologic conditions. The abdomen protruded slightly, and there were physical signs of tympanites. The liver dulness extended from the fifth rib to 2 cm. below the edge of the costal border. The genitalia were negative. The skin was soft, elastic, warm and of good color.

Laboratory findings on Aug. 13, 1914, showed *B. dysenteriae* — Flexner — positive; von Pirquet negative on Aug. 6, 1914.

The blood findings in the case of W. D. may be compared to those of another patient with the toxic type of moderate severity.

CASE 19 (Group 2).—R. G. was the youngest of four children. Her father died at the age of 29 from a paralytic stroke. The brothers and the sister were in good health. The mother gave a history of one miscarriage. There had been no known exposure to tuberculosis or infectious diseases. The child's birth weight was 10 pounds. She had an easy birth, being born at full term without the use of instruments. She was nursed for one month, and then Mellen's food in variable proportions was substituted until the child was 6 months of age. After that time she took bread and crackers and modifications of whole milk.

TABLE 12.—BLOOD FINDINGS IN A CASE OF TOXIC TYPE OF MODERATE SEVERITY

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Türck's Cells
8/ 8/14*	5,800	12	44	40	4	0
8/11/14	8,600	8	20	72	0	0
8/14/14	9,000	6	42	52	0	0
8/17/14	7,600	..	..	..	0	0
8/20/14	6,600	2	64	34	0	0
8/22/14	8,800	2	30	68	0	0
8/25/14	6,800	2	40	58	0	0
8/28/14	6,400	0	50	46	2	2
8/29/14	5,800	2	50	46	2	0

* Entered on the ninth day of illness.

Three weeks before the child was examined, when she was recovering from pertussis, she developed diarrhea. With the diarrhea there were fever and vomiting. Vomiting persisted after the initial attack, being irregular in frequency and occurring immediately after feedings. The amount vomited equaled the amount of food taken, the vomitus being curdled. The diarrhea was very severe, the movements numbering from ten to fourteen a day, green in color, watery in consistency, foul in odor and containing a few curds, much blood and a large quantity of mucus, but the prostration was moderate in degree.

Physical examination showed the child to be of poor development and nutrition. Her general appearance, however, was fair. Her head was round, the posterior fontanel was closed and there was no craniotabes present. The anterior fontanel measured 3.5 by 3 cm. The pupils were clear and responded to light and accommodation. The tongue and mouth seemed normal. The throat was clean and there was no evidence of dentition. There was no discharge from the ears; the glands were negative. Heart, lungs, abdomen and genitalia gave no evidence of a pathologic condition. The liver was slightly enlarged and was 2 cm. below the costal border. The reflexes were present, but not exaggerated. There was no paralysis or muscular spasm, and Kernig and Babinski signs were

absent. The skin was dry, soft and elastic. She had a slight erythema on her back and her buttocks were excoriated.

On Aug. 12, 1914, laboratory examination showed *B. welchii* triple plus.

CASE 23 (Group 3).—E. B. was the youngest child of healthy parents of French extraction. The other children were in good health. The family history was entirely negative. The child was born at full term and was normal at birth. The mother thought the child weighed 7 pounds at birth. The baby, unfortunately, received no breast milk. A modification of whole milk of the formula 2-6-1.6 was given her for two weeks. This, however, did not agree with her. Malted milk was next tried in varying proportions, and the child seemed to thrive much better.

TABLE 13.—LABORATORY FINDINGS IN THE CASE OF R. G.

Date	Leukocytes	Large	Small	Transitionals	Neutrophils	Myelocytes
8/12/14	9,400	2	50	2	46	
8/13/14	17,600	12	54	..	34	
8/15/14	10,800	2	26	4	62	6
8/19/14	18,000	2	82	..	16	
8/21/14	13,600	4	60	..	34	
8/24/14	20,500	4	86	..	10	
8/26/14	16,400	4	50	..	56	
8/29/14	9,400	..	40	..	60	

TABLE 14.—LABORATORY FINDINGS IN THE CASE OF E. B.

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Eosinophils	Türck's Cells
8/13/14	10,200	0	40	60			
8/15/14	30,400	12	36	52	4		
8/19/14	16,800	4	28	76	2		
8/21/14	15,000	2	34	64			
8/24/14	12,400	2	60	36	..	2	
8/26/14	14,200	4	56	36	4		
8/29/14	14,000	2	52	44	..	..	2

Two days prior to admission the child started to vomit forcibly, and each spell of vomiting was accompanied by a dejection. This occurred with each feeding. At the time of entrance the diarrhea was marked, there being from eight to ten dejections, containing the usual ingredients of an infectious diarrhea stool, namely, blood, pus and mucus. Her prostration was slight. She had some fever, but she slept fairly well; her appetite was variable.

Physical examination showed that considering the poor way in which she had been nourished in the past, her development and nutrition were fairly good. Her general appearance and color, while not normal, had not the aspects of a serious infection. The anterior fontanel was still open, otherwise the head was normal. Rigidity and retraction of the neck were negative. There were not as yet any of the signs of rickets. The pupils and the eyes in general seemed normal. The tongue was slightly coated and mouth was clean. There were no

teeth present. Glandular enlargement was not present. The heart, lungs and liver were negative. The abdomen was somewhat pendulous. The reflexes were diminished. No edema was present. The skin was clear, clean, flaccid and smooth.

Examination of stools made Aug. 15, 1915, showed the presence of *B. welchii* and streptococci.

SUMMARY

Total Leukocyte Counts (Weekly Average)

1. There was a progressive weekly increase in the total leukocyte count.

2. Contrasted with this fact, there was a corresponding fall in the temperature.

3. The range of the leukocyte count was least with Flexner bacillus infection and greatest with the mixed infection.

4. Group 1 is characterized by having a normal leukocyte count at the onset, followed within from two to four days by a marked leukopenia, which persists until the convalescent period, unless there are complications. (The normal blood count is from 9,000 to 11,000 [Hayem] for children between the ages of 6 months and 5 years.) Group 2 is characterized by a rather high leukocyte count throughout the illness. Group 3 shows a marked leukocytosis from the beginning, slightly decreasing toward the middle of the illness, but always showing an increased cell count. If one of the organisms is the typhoid or paratyphoid bacillus, combined with *B. welchii*, then the leukocytosis will be diminished; but, on the other hand, if the *B. welchii* is combined with streptococci, a greater leukocyte count than Group 2 will be noticed.

Differential Counts

Group 1 (Sixteen Cases, B. dysenteriae, Flexner)

1. High neutrophilic count for the first two weeks, with corresponding low, small mononuclear count.

2. Large mononuclears increased throughout.

3. Rarity of eosinophils and basophils.

4. Slight increase in neutrophils and a slight decrease of the small mononuclears for the third and the fourth week.

5. Generally a rise follows a remission of the neutrophils and vice versa for the lymphocytes.

6. Myelocytes were present in five cases.

7. Transitional cells were present, particularly when a toxic element was in evidence.

Group 2 (Five Cases, B. welchii)

1. Slight increase of neutrophils.

2. Absence of eosinophils.

Group 3 (Four Cases, Mixed Infection)

1. A small increase in the neutrophils, and a corresponding decrease in the small mononuclears.

2. The large mononuclears show a greater increase than in the two previous groups.

Average Differential Counts, Groups 1, 2 and 3

(Twenty-Five Cases)

1. Large mononuclears increased throughout.

2. Transitional cells are found in about 30 per cent. of the cases, particularly in Group 1 (severe and mild type).

3. Practical absence of eosinophils and basophils.

4. Presence of the so-called Türck's cell in about 20 per cent. of the cases.

5. Large mononuclears, giant cell types, were seen frequently in about 25 per cent. of the cases. They were, however, but few in number. The nuclei were deeply stained by both Giemsa's and Wright's stains.

6. Small mononuclears, Türck's[32] cells, were present. Schleip called my attention to a cell somewhat larger than the small mononuclear and having in addition more protoplasm and less nucleus.

7. Neutrophils showed in many instances a slight degree of transition, but not sufficient to classify them in this group.

8. Basophils were not present.

9. Eosinophils were present in a small number of cases.

10. Transitional cells were present in cases in which the toxemia was more pronounced.

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32. My attention was called to these cells while reading a book by Schleip (Footnote 26). Personally, I do not see a sufficient reason for a separate division; these were simply recorded as a matter of interest.

THE SPECIFIC DIAGNOSIS OF TUBERCULOUS MENINGITIS

A PRELIMINARY COMMUNICATION *

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The pathology of the cerebrospinal fluid in cases of tuberculous meningitis has been the object of intense study in recent years. However, the diagnostic value of examinations of that fluid simply by chemical and cytologic methods is of only relative importance. The most reliable test is to find tubercle bacilli in the cerebrospinal fluid; but that is microscopically often so difficult that in most cases no satisfactory result can be obtained. Consequently, the necessity arises of performing animal injections to confirm the diagnosis. But it is well-known that a comparatively long time, even more than three weeks, is required to determine the result of the experiment. For this reason the method has been abandoned. It is also well known that the presence of the tuberculosis organism produces three kinds of reaction to tuberculin injection, namely, (1) general reaction, (2) focal reaction and (3) local reaction. The focal reaction may well be adopted to diagnose tuberculous diseases, but there is no record of an instance of that reaction being used as a diagnosis of tuberculous meningitis. It seems worth while, therefore, to report the following cases, even though they are small in number.

The diagnosis of tuberculous meningitis by the focal reaction of tuberculin is simple but specific in nature. The process is as follows: After taking out a certain quantity of cerebrospinal fluid by lumbar puncture for cytologic examination, an intradural injection of diluted tuberculin (Koch's old tuberculin) is made. After six, twelve or twenty-four hours cytologic examination is again made of the fluid, which is obtained by lumbar puncture, and a comparison is made of the cell count before and after the intradural injection. The dose of tuberculin injected into the spinal canal is from 0.01 to 0.002 mg., with which a satisfactory result can be obtained. In the preparation of the tuberculin it is well to dilute it with physiologic salt solution (from 0.5 to 1 c.c.).

In this way I have examined the cerebrospinal fluids nine times in five cases of tuberculous meningitis, the result of which I have summarized in Table 1.

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* From the Department of Pediatrics of the Medical College, the Kyoto Imperial University.

TABLE 1.—RESULTS OF CEREBROSPINAL FLUID EXAMINATION FOLLOWING TUBERCULIN INJECTION IN FIVE CASES OF TUBERCULOUS MENINGITIS

Case No.	Name	Age, Years	Nervous Symptoms	Cerebrospinal Fluid	Dose of Tuberculin, Mg.	Cerebrospinal Fluid After the Intradural Injection of Tuberculin
1	H. O.	3	Nausea; vomiting; tremor; convulsions; stiffness of neck; limbs rigid; Kernig's sign	Slight turbidity; albumin 0.079%; globulin +; lymphocytes 38; polymorphonuclears 118; red cells 60	0.001	After 12 hours: albumin 0.089%; lymphocytes 150; polymorphonuclears 330; red cells 3,200 After 24 hours: albumin 0.089%; lymphocytes 310; polymorphonuclears 215; red cells 585
2	K. Y.	5	Vomiting; apathy; nystagmus; rigidity; Kernig's sign; delirium; stiffness of neck	Turbid: albumin 0.148%; globulin +; lymphocytes 123; polymorphonuclears 40; red cells 0	0.002	After 24 hours: albumin 0.156%; lymphocytes 237; polymorphonuclears 130; red cells 53 After 36 hours: albumin 0.151%; lymphocytes 193; polymorphonuclears 97; red cells 7
3	M. Y.	1	Vomiting; apathy; convulsions; limbs rigid; Kernig's sign; stiffness of neck	Slight turbidity; albumin 0.102%; globulin +; lymphocytes 104; polymorphonuclears 8; red cells 0	0.001	After 6 hours: albumin 0.247%; lymphocytes 190; polymorphonuclears 16; red cells 352
4	S. T.	2	Headache; nausea; vomiting; coma; head retraction; convulsions	Slight turbidity; albumin 0.095%; globulin +; lymphocytes 50; red cells 5	0.001	After 24 hours: albumin 0.165%; lymphocytes 910; polymorphonuclears 525; red cells 395
5	T. M.	1½	Vomiting; stiffness of neck; apathy; convulsions; limbs rigid	Turbid; albumin 0.11%; globulin +; lymphocytes 140; red cells 0	0.01	After 12 hours: lymphocytes 855; polymorphonuclears 46; red cells 193 After 24 hours: lymphocytes 716; polymorphonuclears 9; red cells 100 After 72 hours: lymphocytes 164; polymorphonuclears 0; red cells 10

In the examination of the cerebrospinal fluid attention was paid also to an estimation of the pressure, the number of cells per cubic millimeter, the types of cells and an estimation of the globulin and albumin content. For cytologic examinations the Fuchs-Rosenthal method (modified) was adopted. For estimating the albumin I used the nitric acid ring when it was first formed, while globulin was tested by Noguchi's butyric acid method.

As Table 1 shows, tuberculous meningitis gives specific reactions to the intradural injection of tuberculin; in other words, cytologic examination after tuberculin injection shows an increase in the number of cells in general. Chiefly, there are a remarkable appearance of red cells, a considerable increase in the lymphocytes, and a moderate increase in the polymorphonuclear leukocytes. A large percentage of red cells in the cerebrospinal fluid is a significant phenomenon which needs much attention. It is due to hyperemia owing to the reactive nature of the pia mater. In the case of tuberculous meningitis, the cerebrospinal fluid after the intradural injection is remarkably turbid macroscopically and even yellowish in color occasionally.

For a comparative study I tried the intradural injection of tuberculin (from 0.01 to 0.001 mg.) in children with suppurative meningitis, epidemic cerebrospinal meningitis, and with chronic hydrocephalus, but I saw no change of the cells in the cerebrospinal fluid (Table 2).

TABLE 2.—Results of Cerebrospinal Fluid Examination Following Tuberculin Injection in Cases of Hydrocephalus and Nontuberculous Meningitis

Case No.	Name	Age	Diagnosis	Cerebrospinal Fluid	Dose of Tuberculin, Mg.	Cerebrospinal Fluid After the Intradural Injection of Tuberculin
1	S. H.	11 mo.	Suppurative meningitis	Turbid; albumin 0.462%; globulin +; lymphocytes 1,450; polymorphonuclears 1,765; red cells 15; streptococci present	0.001	After 24 hours: albumin 0.412%; lymphocytes 420; polymorphonuclears 720; red cells 10
2	F. Y.	3 yr.	Chronic hydrocephalus	Clear; colorless; albumin 0.02%; globulin —; lymphocytes 4; polymorphonuclears 0; red cells 10	0.01	After 24 hours: albumin 0.021%; lymphocytes 4; red cells 1
3	S. T.	8 yr.	Epidemic cerebrospinal meningitis	2/24. Turbid; albumin 0.214%; globulin +; lymphocytes 136; polymorphonuclears 1,860; red cells 5,580 meningococci present	0.002	After 24 hours: albumin 0.198%; lymphocytes 130; polymorphonuclears 1,860; red cells 4,800
				3/2. Turbid; albumin 0.132%; globulin +; lymphocytes 142; polymorphonuclears 954; red cells 40	0.002	After 24 hours: albumin 0.0825%; lymphocytes 145; polymorphonuclears 594; red cells 5
				3/7. Turbid; albumin 0.1089%; globulin +; lymphocytes 96; polymorphonuclears 536; red cells 0	0.01	After 24 hours: albumin 0.0297%; lymphocytes 94; polymorphonuclears 500; red cells 0

SUMMARY

The diagnosis of tuberculous meningitis by the intradural injection of tuberculin is specific but very simple. Among specific reactions, the most conspicuous thing is an increase in the cell count of the cerebrospinal fluid, especially that of the red cells.

I may add that as my studies are continued I shall in future have the pleasure of forwarding further reports on this subject.

DIABETES MELLITUS IN CHILDREN

REPORT OF TWO CASES WITH A STUDY OF THE URINARY NITROGEN *

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Frequency.—From time to time reported cases of diabetes in childhood have been collected, the first such collection having been made by Kulz in 1878, and the last by Morse[1] in 1913. There are now on record more than 1,000 cases, in which an equal distribution between boys and girls and an incidence increasing with the age are observed. Though over 100 cases in children under 1 year of age have been reported, there is nothing in the majority to show that the sugar was glucose, and it is quite probable that many of these were cases of lactosuria. Knox,[2] in going over the literature in 1911, could find but 16 cases which he regards as true diabetes. In Morse's collection there are 200 children under 5 years of age, which, considering the time period covered by the survey, makes the disease at this early age almost a rarity. It has been estimated that among diabetics of all ages, the childhood incidence is about 2 per cent.

Prognosis.—The prognosis in children has been regarded by all writers on the subject as grave, no matter how mild in the beginning or how gradual in development. Among the collected cases there are twenty-six patients reported as recovered, but the proof of recovery is satisfactory in less than ten, one third of the cases having been followed but three months or less. On the basis of ten recoveries in one thousand cases there has been a mortality of 99 per cent.

The Allen Treatment.[3]—No one can say what is now the ultimate prognosis of diabetes in childhood under the new régime which more than vaguely promises a long life of good health if not a permanent cure. There are no case reports of children under this new régime to show even its immediate effects. Since the publication of Allen's work there have come under our observation two cases of diabetes mellitus in childhood which will be reported in detail.

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* Submitted for publication Dec. 10, 1916.

* From the Department of Pediatrics, Washington University Medical School, and St. Louis Children's Hospital.

1. Morse, J. L.: Boston Med. and Surg. Jour., 1913, **168,** 530.
2. Knox, J. H. Mason, Jr.: Bull. Johns Hopkins Hosp., 1913, **24,** 274.
3. Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Harvard Univ. Press, Cambridge, Mass., 1913; ibid., Jour. Am. Med. Assn., 1914, **58,** 539; ibid., Boston Med. and Surg. Jour., 1915, **172,** 241; ibid., Am. Jour. Med. Sc., 1915, **150,** 480; ibid., Boston Med. and Surg. Jour., 1915, **173,** 743.

REPORT OF CASES

CASE 1.—The patient was a girl 2 years of age.

Family History.—The father, mother and one older child are all in good health and there is no history of diabetes in the family.

Past History.—The patient was born spontaneously at term, was breast fed, and developed normally both mentally and physically. There has been no illness except as is mentioned below.

Present Illness.—The patient first came under observation Dec. 30, 1914, for frequency of urination, which had been present for three weeks following an intestinal disturbance. She received treatment for this condition for one month, with improvement. During this month of observation she gained in weight from 11.15 to 11.94 kg. and three urine examinations showed nothing abnormal. She again came under observation May 11, 1915, with the history of having had measles during the latter part of March, with which she had been very ill for three weeks. The urine was not excessive or troublesome before the measles, but did become so immediately afterward. At this time the mother noticed that the diapers were sticky, and a few days later sugar was found in the urine by the family physician. The polyuria was associated with greatly increased thirst, demanding water numerous times during the night. Sleep was broken and restless. When obtained on May 11, the urine caused abundant reduction of Fehling's solution and fermented with yeast. The child was admitted to the St. Louis Children's Hospital May 22, 1915, at which time the general physical examination revealed nothing of importance. She was exceedingly well nourished and did not appear ill, though she was irritable and had general malaise. The Wassermann reaction was negative. Her weight on admission to the hospital was 11.6 kg. and her age was 26 months.

Progress.—On the regular hospital diet the patient excreted 46 gm. of sugar in twenty-four hours. With the institution of fast she became sugar-free in the first twenty-four hours and at the same time her increased thirst disappeared and the amount of urine decreased abruptly from 1,500 c.c. daily to 700 c.c., and later to much less than this. She slept well at night and her general disposition improved. With a gradual increase in the diet over a period of three weeks, she showed glycosuria on a diet having a value of 870 calories and including 22 gm. of carbohydrate. Following another fast day she remained sugar-free on various diets (Table 1) until she was discharged from the hospital, Nov. 24, 1915. The successful handling of several of these diets indicates an increase in her tolerance. Her diet at home was practically a constant one and she remained sugar-free and in good health for a month, when she returned with an acute bronchitis and a slight glycosuria. The bronchitis was rather severe and there was considerable fever for three days. On readmission to the hospital, Dec. 17, 1915, she received, by mistake, a diet slightly in excess of the previous allowance, and yet the urine became sugar-free, with improvement of the acute infection. She was discharged December 24 with a lower diet. The urine was examined almost daily and sugar was found on March 8 and March 14, 1916. She had been having a carbohydrate free diet one day each week. The patient was readmitted to the hospital March 15, 1916, when she was again fasted and discharged with a lower diet. She remained sugar-free and free from complaints until Nov. 7, 1916, when, associated with a slight indigestion and a coryza, she again had a small amount of sugar in the urine. She is now sugar-free and in good health. Her weight in November, 1916, was 13.6 kg.

Discussion of Case 1.—The criteria of the condition of a diabetic are the amount of sugar in the urine and blood and the degree of acidosis. The degree of acidosis may be measured in a variety of ways, but the common methods, and the ones used in these cases, are the

amounts of acetone bodies excreted in the urine and the urinary ammonia coefficient. At no time was the acidosis of such a degree as to give distinct clinical manifestations, though during all observation periods the amount of acetone bodies in the urine was definitely increased above the normal. During the last period the amounts were strikingly less than before. Following each fasting period there occurred a marked increase in the acetone bodies, which made but a short curve, quickly returning to a lower level as food was allowed. This increase was rather to be expected, but the decrease which occurred in every instance on the day of fast seemed unusual and is in distinct contrast to the behavior of the normal child. This phenomenon might be the object of considerable speculation, though the most plausible explanation would seem to be the sudden withdrawal of protein with its acetone body precursors, together with the availability of stored glycogen in sufficient amounts to protect the normal combustion of fats. As the stored glycogen decreases, there occurs an increase in acetone bodies, as in any other patient. The more acetone body formation is studied the more complicated does the question become, and whether or not this phenomenon is to be explained in this way, the fact itself is of interest.

The ammonia followed the acetone curve fairly closely, though it seemed somewhat delayed in excretion. At all times the ammonia coefficient was found increased over that found in normal children. During the last period the ammonia, as well as the acetone bodies, was lower than in previous periods, which is encouraging in the prognosis for this patient.

The values given in the accompanying tables for blood sugar are lower than other published observations, probably due to the method employed. The method followed was that of Shaffer,[4] who, in his paper, discusses the difference in results by his method and by previously published methods. Whatever criticism may be directed against any method in current use as being an absolute measure of blood sugar, still leaves that method of value in determining comparative results. To determine the normal value by this method a number of presumably normal children from 2 to 3 years of age were selected and blood samples were taken after a night of fast and before breakfast. The normal values thus obtained varied closely in the neighborhood of 0.05 per cent. If the sample was taken later in the day, after food had been given, the values were higher. The figures in the accompanying tables represent the morning fasting values.

Relatively few observations have been made of the blood sugar in this patient, but there is a sufficient number to show that there has

4. Shaffer, P. A.: Jour. Biol. Chem., 1914, **19,** 285.

TABLE 1.—DATA—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbohydrate	Alcohol	Total	Per Kilo	
May 25*	..	..	..	..	.....	..	.....
27	65	34	27	0	855	73	11.66
28	65	34	27	0	855	73	.....
31	87	42	30	0	1,110	97	11.38
June 1	87	42	30	0	1,110	97	.....
2	0	0	0	25	175	15	.....
3	21	5	0	0	215	20	.....
4	43	14	4	7	520	47	.....
5	41	19	13	9	575	53	10.83
7	54	25	13	9	720	68	10.63
9	54	25	13	9	720	68	10.60
11	54	25	13	9	720	66	10.91
12	54	25	13	9	720	65	11.08
15	64	32	13	9	840	78	10.86
18	68	35	18	4	880	81	10.89
21	72	39	22	0	870	78	11.14
23	0	0	0	25	175	16	11.14
24	17	4	0	16	285	26	10.89
26	51	21	13	13	705	67	10.52
28	55	20	16	11	735	71	10.40
30	66	25	13	11	850	80	10.69
July 2	76	32	13	9	950	89	10.66
5	76	32	13	9	950	87	10.89
9	76	32	13	9	950	88	10.86
16	76	32	13	9	950	88	10.77
20	76	32	13	9	950	85	11.14
23	76	32	13	9	950	85	11.25
27	76	32	13	9	950	87	10.97
Aug. 5	76	32	13	9	950	87	11.00
7	80	35	18	4	995	90	11.05
12	84	39	22	4	1,060	93	11.43
Sept. 8	84	39	22	4	1,060	91	11.66
20	84	39	22	4	1,060	89	11.96
28	76	29	27	4	965	81	11.99
Oct. 9	76	29	27	4	965	80	12.04
11‡	80	35	18	0	970	85	11.43
21	80	35	18	0	970	81	11.99
29	80	35	18	0	970	80	12.07

* Hospital diet.
† The heading "Acetone" includes diacetic acid. Beta-oxybutyric acid is recorded as acetone.
‡ Oct. 10, 1915, was a fast day.

—OF CASE 1

Blood Sugar, per Cent.	Urine				Urinary Nitrogen				
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.
.....	1,020	46							
.....	1,480	14	...	.....	5.01	1,080	55	..	49
.....	1,490	14	...	.....	5.40	930	53		
.....	1,300	23	487	1,157	5.41	820	46	39	63
.....	1,485	27	438	1,276	4.48	850	47	45	38
.....	700	0	...	.....	2.49	300	36	..	40
.....	715	0	240	1,024	1.93	300	28	38	25
.....	765	0	360	1,590	2.63	500	37	38	53
0.045	880	0	310	1,440	3.26	600	36	46	45
.....	935	0	140	430	3.34	600	34	39	38
.....	715	0	120	140	2.24	300	25	35	43
.....	705	0	200	230	3.21	410	32	42	51
.....	555	0	60	140	1.85	200	27	29	38
.....	555	0	160	620	2.36	360	28	35	41
0.057	580	0	160	670	4.10	670	38	42	65
0.068	675	1	287	590	4.59	370	52	57	59
.....	875	0	87	160	2.52	480	47	49	50
0.030	625	0	350	2,300	2.72	510	41	72	29
.....	520	0	320	1,320	2.14	620	34	38	60
0.047	735	0	220	770	2.68	770	41	39	49
.....	545	0	106	300	1.88	354	31	32	35
.....	495	0	131	463	3.09	390	31	41	45
.....	605	0	188	658	2.84	418	27	48	45
.....	510	0	125	378	2.91	304	..	..	44
.....	375	0	454	1,040	2.65	.....	43	55	54
.....	525	0	131	361	3.05	367	32	49	41
.....	410	0	227	439	2.20	340	25	34	21
.....	390	0	226	480	2.60	557	36	39	31
.....	660	0	545	1,240	3.20	702	33	38	32
.....	550	0	...	.....	2.54	495	34	..	38
.....	525	0	131	400	2.40	327	31	..	35
.....	400	0	180	870	2.63	567	41	32	
.....	500	0	110	423	3.01	387	37	52	33
.....	610	0	137	200	3.77	423	49	67	47
0.061	330	0	201	975	2.40	293	35	46	40
.....	460	0	722	2,400	4.09	968	46	79	68
.....	295	0	94	280	2.95	300	28	41	32
.....	350	0	222	890	2.25	287	32	49	37

TABLE 1.—DATA OF—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbohydrate	Alcohol	Total	Per Kilo	
Nov. 19	80	35	18	0	970	78	12.48
Dec. 18	84	39	22	26	1,235	..	.....
20	84	39	22	26	1,235	100	12.39
21	0	0	0	25	175	14	12.24
23	84	34	13	0	980	80	12.28
1916 Mar. 16	80	35	18	0	965	73	13.14
17	0	0	0	25	175	..	.....
18	65	20	20	0	765	..	.....
19	65	20	20	0	765	59	13.05
21	65	20	30	0	810	62	13.14
22	65	20	40	0	850	65	13.14
23	65	20	50	0	890	68	13.17
24	65	20	60	0	930	70	13.22
25	0	0	0	25	175	13	13.25
26	35	13	10	0	420	..	.....
27	65	20	20	0	770	59	12.94

TABLE 2.—DATA—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbohydrate	Alcohol	Total	Per Kilo	
Nov. 25*	..	..	..	..	.....	..	.....
27	69	38	31	0	925	56	16.14
28	69	38	31	0	925	..	.....
Dec. 1	77	45	40	0	1,065	67	15.91
2	81	48	45	0	1,135	71	15.91
3	81	48	55	0	1,175	73	16.19
4	81	48	66	0	1,215	74	16.39
5	81	48	75	0	1,255	76	.....
6	0	0	0	24	170	10	16.00
7	13	3	0	6	175	11	15.70
8	55	20	16	9	675	44	15.43
10	66	26	13	9	835	53	15.67
12	76	32	13	9	955	61	15.64
14	80	36	18	0	965	61	15.75
17	84	39	22	0	1,035	66	15.72
20	84	41	22	0	1,040	67	15.61

* Hospital diet.
† The heading "Acetone" includes diacetic acid. Beta-oxybutyric acid is recorded as acetone.
‡ The blood sugar is charted opposite the diet which it represents. The determination was made the day following.

—CASE 1—(*Continued*)

Blood Sugar, per Cent.	Urine				Urinary Nitrogen					
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.	Urea N, Gm.
0.054	430	0	267	895	3.37	537	44	60	31	
.....	345	2	400	1,350						
.....	340	0	272	650	3.88	467	40	57	50	
0.089	375	0	160	574	2.14	234	39	45	34	
.....	250	0	557	884	2.92	610	32	50	64	
0.071	850	0	520	2,090	4.55	589	48	72	28	3.35
.....	500	0	95	234	2.49	413	41	64	47	1.53
0.041	345	0	46	1,610	3.82	700	43	73	46	2.45
.....	300	0	353	1,160	3.31	667	39	52	52	1.92
.....	325	0	85	103	3.07	431	44	53	77	2.01
.....	210	0	70	149	2.48	266	45	53	58	1.73
.....	355	0	50	55	2.24	200	43	58	58	1.52
.....	380	0	52	50	2.27	194	45	55	54	
0.060	315	0	24	35	1.73	156	41	46	41	
.....	345	0	98	214	2.76	251	50	67	53	
.....	525	0	180	440	2.50	309	42	49	43	

—OF CASE 2

Blood Sugar,‡ per Cent.	Urine				Urinary Nitrogen				
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.
.....	810	40	255	846	6.30	494	126	208	93
.....	535	0	410	1,720	5.92	571	81	130	84
0.057	660	0	235	709	6.76	870	84	117	131
0.053	705	0	220	16	5.92	422	77	55	95
.....	665	0	145	88	5.99	395	70	61	108
0.062	565	0	80	71	6.06	349	86	55	99
0.074	860	0	70	55	6.80	379	98	59	102
0.063	605	1	45	22	4.78	277	59	61	82
0.034	805	0	280	66	5.03	251	86	47	90
0.035	430	0	219	900	4.21	255	48	95	48
0.059	455	0	420	2,400	4.44	454	67	87	72
0.049	500	0	154	242	....	293	65	..	60
.....	650	0	205	431	4.41	474	57	50	58
0.058	655	0	108	270	4.03	377	71	32	64
0.052	490	0	81	157	5.88	471	..	27	77
0.050	350	0	153	272	3.60	285	64	29	33

been at no time after starting treatment a very marked hyperglycemia. It is generally stated that the blood sugar of normal individuals does not decrease appreciably below the normal level with a short fast, and such also has been our experience. It is stated, also, that a high blood sugar in diabetes is not lowered as quickly as in normal subjects, though a subnormal drop in blood sugar following fast is very noticeable in this patient.

At the beginning of observation this patient had an average body weight for her age, 11.6 kg. During the first year of observation there was a gain of 1.4 kg., and during the first six months of the second year there has been a gain of 0.6 kg. There has been a considerable increase in her body length, and it is evident that her growth has been at the expense of her stores of body fat. She is now below the average weight for her age.

Summary of Case 1.—A moderately severe case of diabetes mellitus in a 2-year-old girl, coming under observation early and remaining under observation one and one-half years, was made sugar-free by an initial fast, and remained sugar-free throughout the observation period except for five occasions. One of these was due to intentional overfeeding, and another was the result of an acute infection. The other three occasions were transient and occurred only on the days mentioned. There has been complete relief of the subjective symptoms and the polyuria, and there is considerable evidence that her tolerance has increased. At no time was the evidence of acidosis sufficient to draw any especial attention to it. Though she is by no means cured, there seems to be no good reason why she should not have a long life, free from diabetic symptoms.

CASE 2.—The patient was a boy aged 3 years.

Family History.—The father and mother and the child of the first pregnancy are in good health. A Wassermann reaction on the mother was negative. The second and fourth pregnancies resulted in miscarriage. The fifth pregnancy resulted in a premature birth at six and one-half months, the child of which died of bronchopneumonia at 9 months.

Past History.—The patient was the child of the third pregnancy and was delivered by means of forceps at term. He was normal at birth and continued so for several months. From the age of 6 months he was frequently brought to the Children's Hospital dispensary for various minor ailments. During infancy he was an overfed, condensed milk baby, fat, but having recurring attacks of diarrhea, with one of which at 21 months he had two convulsions. Condensed milk was continued both with this baby and the succeeding one, contrary to all advice, which illustrates the parental attitude to our instruction. The patient cut his teeth, walked and talked at the usual age. There was an acute bronchitis at 18 months and again at 2 years. Aug. 16, 1915, he became ill with measles, which ran a mild course.

Present Illness.—He was admitted to the Children's Hospital, Nov. 25, 1915, having had polyuria and increased thirst for two weeks. These symptoms were associated with loss of appetite, slight loss of weight and a definite bread hunger. There were no other complaints.

Examination.—The patient was well nourished and apparently in good health. There were several features that suggested dyspituitarism. The hands were spade-like and the skin was dry. The fingers were of the shape seen in acromegalics. The hands and feet were large and the stature was somewhat above the normal. Roentgenograms of the sella turcica and of the feet and hands showed no abnormalities.

Progress.—On the regular hospital diet the patient excreted 40 gm. of sugar in twenty-four hours. On restricted diet without fast he became sugar-free in the first twenty-four hours, and with a gradual increase in the diet he again had glycosuria when the diet reached the value of 76 calories per kilogram and included 75 gm. of carbohydrate. Following a fast he became sugar-free and remained so on his subsequent diet until April 3, 1916, a period of four months. After this time the parents refused to keep him under supervision and the dietary restrictions were largely removed. He is said to have remained in good health until June 1, 1916, when he became ill. June 2 he was admitted to the Children's Hospital in coma. At this time he had deep, pauseless respirations at the rate of 52 per minute, his temperature was 102.4 F., and there were râles at the bases of both lungs. Following the intravenous administration of 150 c.c. of 4 per cent. sodium bicarbonate solution, the respiratory rate decreased to 36, the patient recognized his mother and held simple conversation. Four hours later he was again comatose and the respiratory rate was 70. Following intravenous administration of sodium bicarbonate he became more quiet at once, and at no time later did he show air-hunger breathing. The urine for twenty-four hours, from June 2 to 3, measured 100 c.c., and showed much albumin and many casts. There was no sugar. The ammonia nitrogen was 24 per cent. of the total nitrogen. The urine for twenty hours from June 3 to 4 measured 465 c.c. and showed much albumin and many casts. There was 1.2 gm. sugar and the ammonia nitrogen was 12 per cent. of the total nitrogen. Examination of the blood on June 3 showed, per 100 c.c., 103 mg. of nonprotein nitrogen, 38 mg. of acetone and diacetic acid and 75 mg. of beta-oxybutyric acid (as acetone). The blood sugar was 0.3 per cent. The blood on June 4 showed, per 100 c.c., 41 mg. acetone and diacetic acid and 107 mg. beta-oxybutyric acid (as acetone). The blood sugar was 0.4 per cent. The white cell count on June 3 was 60,000, of which 70 per cent. were polymorphonuclear cells. Death occurred on June 4, being preceded by several clonic convulsions. A necropsy was refused.

Discussion of Case 2.—When this patient first came under observation there was some question as to whether the case was one of true diabetes or a transient glycosuria. Though he had a high tolerance for carbohydrate, there was considerable evidence in favor of the diagnosis of diabetes. There was at all periods except one a distinct tendency toward acidosis, as shown by the laboratory findings. In the twenty-four-hour period which makes the exception he received 75 gm. of carbohydrate and showed a glycosuria. He showed a hyperglycemia while receiving from 55 to 75 gm. of carbohydrate in twenty-four hours, and a fairly marked subnormal drop in blood sugar following fast. The twenty-four-hour amount of urine was not excessive, but he was removed from the regular hospital diet and routine so quickly after admission that this point was not well determined. There was a definite polyuria before admission. The thirst and polyuria quickly disappeared under treatment, but the bread hunger remained.

The marked increase in the acetone bodies on the day of fast differs

from Case 1 and corresponds to the normal child. Otherwise the figures for the acetone bodies and for ammonia are similar in kind though not in degree to those of Case 1.

Up to April, 1916, at which time his visits ceased, the prognosis seemed good. As Allen states, there are two factors which determine the success of treatment, the scientific and the human factor. In Case 1 the human factor is found at its best, while in Case 2 this factor was apparently the point of failure, this being by far the milder of the two cases. The scientific factor was the same in both instances.

Aside from possible pneumonia, there is evidence that the death of this patient was due to two factors, acidosis and uremia. When observed in April the urine was free from albumin, but previous to his death both the urine and the blood showed evidence of a nephritis with retention of nonprotein nitrogen. The alkali therapy relieved the acidosis to some extent, but had little effect on prolonging his life.

Summary of Case 2.—A mild case of diabetes in a 3-year-old boy coming under observation two weeks after the onset of symptoms. Merely lowering the diet was sufficient to make the urine sugar-free. There was relief of the polyuria and subjective symptoms, except bread hunger, by regulation of the diet. He remained sugar-free and in good health during the four months of observation. Following this the dietary restrictions were broken and death occurred six and one half months after the onset from acidosis and uremia.

Diet.—In spite of Allen's statement that we should be governed by no theoretical standards of calories or protein, but rather by the individual tolerance for each individual food, it is well to have in mind the theoretical considerations that go to make up a well-balanced diet. If the patient's tolerance permits, it would seem better for him to have a well-balanced than a badly balanced diet, and the younger the patient the more important does this become. The protein needs of a child are about 1.5 gm. per kilogram, and this amount constitutes from 9 to 13 per cent. of the total calories. As to the proportion of fat and carbohydrate that should make up the diet, there are no absolute data. Though the diet of a thriving child varies within rather wide limits in different individuals, one, the food value of which beside the protein is equally distributed between the fats and carbohydrates, makes a very good average. Fats and carbohydrates are of almost equal importance as protein sparers. It seems likely that in the young, growing child the body needs are best supplied by having the food value of the fats somewhat greater than that of the carbohydrates, even as much as 25 per cent. greater. In preparing a restricted or minimum diet for a child there should be at least the minimum requirement of protein, 1.5 gm. per kilogram, the fats should be about 50 per cent. and the

carbohydrates about 40 per cent. of the total calories. In many diabetic children this amount of carbohydrate would not be well tolerated, and for this reason it should be decreased and the fat increased sufficiently to meet the needs of the individual patient.

Body Weight.—The question of diet has a very intimate relation to that of body weight. Allen's statement that any increase in body weight that is attended with glycosuria or an increase in the acetone bodies should be checked holds true for children as well as for adults, but apparently little attention is paid to the fact that children are expected to grow. This growth must ultimately involve increase in weight, and it would seem necessary to allow a reasonable increase in weight in any child who remained sugar-free and acetone-free.

NITROGEN DISTRIBUTION IN THE URINE

A study of the urinary nitrogen was made in the two cases of this report, extending over a period of ten months in Case 1, and of one month in Case 2. The total nitrogen, creatin, creatinin, uric acid and ammonia were determined, and in Case 1 the urea was determined during one period.

Creatin and Creatinin.—For the determinations of this report the revised Folin[5] method was employed. No attempt was made to remove the acetone bodies, since in but few, if any, specimens were these substances present in amounts sufficient to interfere with the determination.[6] The diet was at all times such as is usually termed creatin-free and creatinin-free, and consisted of milk, eggs, butter, cream, and, for most of the periods, vegetables.

Since it has been shown that on a creatin-free and creatinin-free diet the excretion of creatin and creatinin is unaffected by the variety or amount of exogenous protein, except as sugar may be obtained from the protein,[7] a diabetic who is sugar-free and therefore utilizing all of the carbohydrate of the diet might be considered as a normal individual as far as creatin and creatinin excretion is concerned, provided sufficient carbohydrate is fed. There is considerable evidence that, in regard to the excretion of these substances, these patients behaved as normal children. At periods in which relatively large amounts of carbohydrate were allowed and apparently utilized, the creatin and creatinin coefficient was not different from that obtained during periods of lower carbohydrate intake. In Case 1 a slightly higher coefficient was obtained in the later than in the earlier periods, probably because

5. Folin, O.: Jour. Biol. Chem., 1914, **17,** 469.

6. Greenwald, I.: Jour. Biol. Chem., 1912-1913, **14,** 87. Graham, G., and Poulton, E. P.: Proc. Roy. Soc., Series B, 1914, **87,** 205.

7. Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1914, **18,** 195.

of the relative decrease in adipose and increase in muscular tissue. Taking 12 kg. as the mean weight for the year in Case 1, the average creatin value as 0.048 gm. and the average creatinin value as 0.037 gm., the coefficient is found to be 4 for creatin, 3.1 for creatinin and 7.1 for their sum. In Case 2 is found a coefficient of 3.2 for creatin, 4.6 for creatinin and 7.8 for their sum. This difference in the total coefficients can easily be accounted for by the relatively larger amount of adipose tissue in Case 1. Several normal children[8] of about the same age while having a creatin-free and creatinin-free diet were found to have a total coefficient of from 7.0 to 7.7, with one exception, which gave a coefficient of 10.

The coefficients of the total creatin and creatinin nitrogen in these patients is practically the same as is found in adults for creatinin nitrogen,[9] a fact not especially surprising. In adults there is a constant daily and even hourly excretion of creatinin for each individual, though varying somewhat in different individuals. One might expect to find this same constancy for children, if not in creatinin, perhaps in the sum of creatin and creatinin. This has never been shown and does not appear in these patients, though the variations in the amounts of these substances found is not remarkable. Every effort was made to obtain exact twenty-four hour specimens.

Uric Acid.—For all periods up to March 17 there was in the diet of Case 1 a small and fairly constant amount of vegetables, consisting largely of spinach and cauliflower, boiled with three changes of water. Otherwise the diet was purin-free. For the last period vegetables were omitted and the diet consisted of cream, eggs and butter. Benedict's modification of Folin's method of determination was employed.[10] At no time was the uric acid excretion very constant nor was there any constant relation to the total nitrogen. However, the variations were within fairly narrow limits. The average daily excretion of uric acid nitrogen for the periods containing some vegetables was 0.043 gm., and for the period of purin-free diet it was 0.050 gm. In Case 2 there were much higher uric acid values, but these can easily be interpreted as partly exogenous. The patient was removed from a generous diet on admission to the hospital and the uric acid excretion during observation, though irregular, showed a decided tendency to decrease. In a small group of normal children[8] from 18 to 24 months of age, whose previous diet had always been low in purins, the average values for uric acid nitrogen on a purin-free diet was found to vary from 0.051

8. These figures were taken from the determinations made by Veeder and Johnston, which are not yet published.

9. Shaffer, P. A.: Am. Jour. Physiol., 1908, **23,** 1.

10. Benedict, S. R., and Hitchcock, E. H.: Jour. Biol. Chem., 1915, **20,** 619.

to 0.055 gm. Children older than this who have been accustomed to meat and other purin-containing foods gave even higher values during short interval observations.

The figures here presented show that the uric acid excretion in the two diabetic patients is practically the same as is found in normal children of the same age under similar dietary conditions, and further show the surprising fact that a child of 12 kg. excretes as much uric acid as an adult.[11]

Urea.—In Case 1 urea nitrogen was determined in the last period, the findings not being remarkable in any way. The amounts found varied from 58 to 74 per cent. of the total nitrogen and showed an inverse proportion to the amounts of ammonia present. In the normal child the ammonia nitrogen varies in the neighborhood of 4 to 6 per cent. of the total nitrogen, and the urea 80 per cent. or more. The increased ammonia values during this period account adequately for the decreased urea.

11. Raiziss, Dubin and Ringer: Jour. Biol. Chem., 1914, **19,** 473.

SYPHILITIC DISEASE OF THE THYMUS IN INFANTS AND THE MODE OF ORIGIN OF THE DUBOIS ABSCESSES*

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Though first described by Cruveilhier[1] in 1829, cysts in the thymus of the new-born were first carefully studied by Dubois[2] twenty-one years later. By this author they were considered abscesses, on account of their purulent contents, and as all of his cases were in infants who showed definite evidences of congenital syphilis, he regarded the condition as of syphilitic origin.

In the following years of gross pathology numerous cases of "abscesses" of the thymus were described, but it was not until the microscopic study of Chiari[3] that the true nature of these structures became known. In a male infant which died a few minutes after birth and which showed pronounced syphilitic lesions (pneumonia alba, hepatitis, pancreatitis, and osteochondritis syphilitica), he found the thymus, which was not enlarged, to be filled with cavities which contained purulent material. Microscopically, however, these cavities proved to be not abscesses, but cystic spaces lined with a definite epithelial covering of a flat stratified type. As there was a marked cystic dilatation of the Hassall bodies, which were filled with leukocytes, Chiari described the larger cysts as arising from these structures by a process of degeneration and ingrowth of small thymic lymphocytes.

Since this time all authors have agreed on the cystic nature of the cavities, while various views as to their mode of origin and significance in regard to syphilis have been held. The small number of true cystic thymuses found since the introduction of the microscope is due to the exclusion of cases of cavitation in the organ due to postmortem changes. Since Chiari's description, I have been able to find but eight cases of true cystic thymuses in infants.

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* From the Pathological Laboratory of the Medical School of Leland Stanford Junior University.

1. Cruveilhier, J.: Anat. Path. du Corps Humain, 1829-1835, Book 15, pl. 2. Obs. 6.

2. Dubois, P.: Du diagnostic de la syphilis considérée comme une des causes possibles de la mort du foetus, Gaz. méd. de Paris, Series 3, 1850, **5,** 392.

3. Chiari, H.: Ueber Cystenbildung in der menschlichen Thymus, Zugleich ein Beitrag zur Lehre von den "Dubois'schen Abscessen," Ztschr. f. Heilk., 1894, **15,** 403.

Schlesinger,[4] in describing the syphilitic lesions found in the thymus, describes one case of a female child that died shortly after birth, in which cysts were present. In detail the findings and conclusions are almost identical with those of Chiari. Tuve[5] has described two cases of cystic thymus in congenitally syphilitic children. Their origin is explained in a somewhat different manner. According to this author there has been a widespread necrosis of the thymic medulla, due to a failure of development of the blood vessels. The persisting reticulum cells have proliferated and formed the epithelial covering of the cyst.

The most detailed study of such cases has been made by Simmonds.[6] Out of 120 thymuses, the author found two which contained large numbers of cysts. In both, spirochetes could be found in the contents of the cysts and in the cyst walls. Another appearance which Simmonds emphasizes is the relative preponderance of the reticular epithelial cells over the small thymic cells. The Hassall bodies were few in number and the whole organ filled with cysts. Three other thymuses from syphilitic infants showed no cysts, but many Hassall bodies and the same preponderance of reticulum cells over the lymphocytes. The author does not believe that the cysts arise from the Hassall bodies, but that there has been a defective development, with syphilis as the causative factor. The failure of development is shown by the undifferentiated appearance of the thymus (preponderance of epithelial cells) and the cysts, which he identifies with the original cavity of the early thymus.

Pappenheimer[7] in his study of the pathology of the thymus describes two specimens from syphilitic infants. One, a 7-months' macerated fetus, contained cysts; their size is not given. The specimen showed a marked preponderance of the reticulum and disappearance of the lymphocytes. Spirochetes could be demonstrated, and there was a marked increase in the perilobular connective tissue. The author says, "the effect of the congenital syphilitic infection in this case at least is not merely an arrest of development, but an actual atrophy or degeneration of the gland with replacement fibrosis." Another case of congenital syphilis showed no cysts or Hassall bodies, but consisted almost entirely of reticular epithelial cells and a few lymphocytes.

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4. Schlesinger, E.: Die Erkrankung der Thymusdrüse bei der hereditären Syphilis, Arch. f. Kinderh., 1899, **26,** 205.

5. Tuve: Ueber die sogenannten Dubois'schen Thymusabscessen, Diss., Leipzig, 1904. (Cited from Simmonds, Note 6.)

6. Simmonds, M.: Die Thymus bei kongenitaler Syphilis, Virchows Arch. f. path. Anat., 1908, **194,** Suppl., 213.

7. Pappenheimer, A.: A Contribution to the Normal and Pathological Histology of the Thymus Gland, Jour. Med. Research, 1910, **22,** 1.

The most recent case is that described by Ribbert.[8] A stillborn infant, showing marked evidence of congenital syphilis, had a thymus of normal size, so filled with cysts that on cutting into it, it collapsed. The cysts were lined with a stratified epithelium similar to that of the pharynx, outside of which was a layer of connective tissue, and exteriorly a layer of lymphocytes, arranged in what might be considered follicles. Ribbert concludes that there can be no question of these cysts arising from the Hassall bodies, but that the similarity of its structure to that of the tonsil shows it to be the primary lumen of the developing thymus which has become cystic.

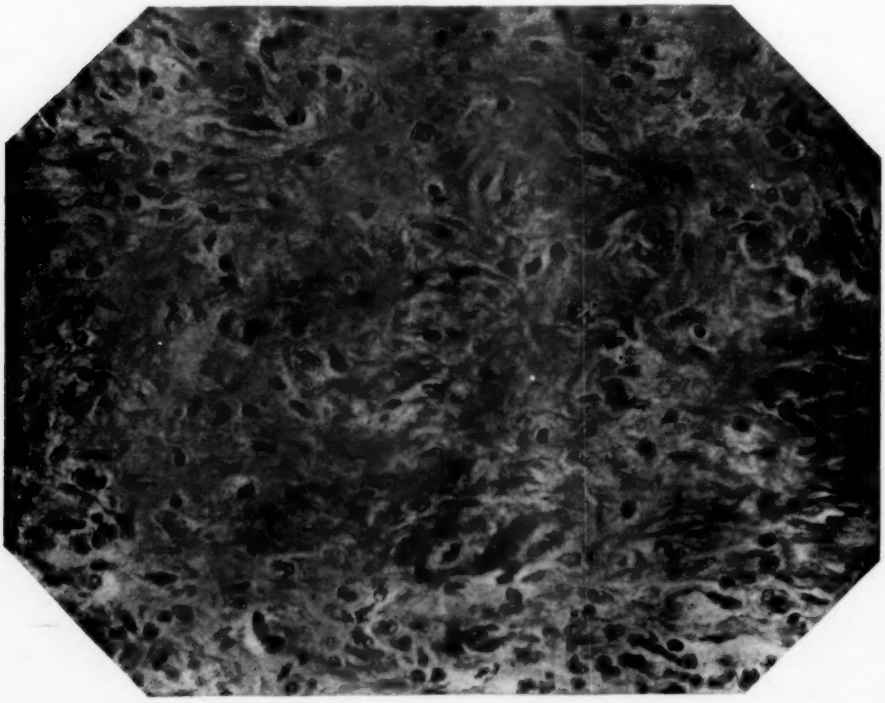

Fig. 1.—Field from the center of a lobule. Nothing remains of the thymus tissue but the shrunken reticulum cells and a few lymphocytes. The main mass of tissue is composed of dense fibrous connective tissue. B. & L. Oc. 1. Obj. ⅙ in.

In reviewing the cases which have been described, we see that all the infants have suffered from congenital syphilis. The cystic nature of the cavities is agreed to by all authors, but the manner of origin is differently described. Chiari and Schlesinger derive them from the Hassall bodies, Simmonds and Ribbert identify them with the primary

8. Ribbert, H.: Die Entwicklungsstörung der Thymusdrüse bei kongenitaler Lues, Frankfurt Ztschr. f. Path., 1912, **11,** 209.

cavity of the developing thymus, while Tuve holds that they arise by a necrosis of the medullary tissue. Another point of interest is the change seen in the thymus tissue as a whole, which has been pointed out especially by Simmonds and Pappenheimer.

REPORT OF CASE

My case is of interest, not only because of the rarity of the disease, but also from the fact that as the process has not gone on to an extreme degree, the manner of origin of the cysts is plainly seen.

Fig. 2.—A part of the largest cyst with its contents of detritus. Along the margin of the cyst is seen the dark band of the lining epithelium, the remnant of the lobule. At the lower border of the figure, the remnant of thymus tissue is considerably thicker and contains some dilated Hassall bodies. The small dark spots in the other lobules show Hassall bodies of normal size. In the upper part of the section note the remnants of a Hassall body which has ruptured into the main cyst. B. & L. Oc. 1. Obj. 1 in.

History.—An Italian girl baby, 6 weeks of age, was brought to Lane Hospital complaining of fever, discharge from the nose and "blisters" on the abdomen. On examination two large blebs were found on the abdomen, rhagades at the mouth, a serosanguineous discharge from the nose, and edema of the hands and wrists. The urine showed a heavy cloud of albumin, many granular casts, and a few red blood cells. Though no syphilitic history could be obtained from the parents, the baby's Wassermann proved positive. The child was placed on mercurial treatment, but five days after admission died with signs of pneumonia.

Necropsy.—At necropsy, without giving the detailed descriptions of the various organs, there was found a pronounced pneumonia alba, osteochondritis

syphilitica, interstitial hepatitis, as well as miliary gummas in the liver, and a subacute glomerulonephritis. The thymus was of normal size, but quite fibrous. The cysts to be described later were not seen in the single cut made through the organ.

Pathologic Histology.—After fixation in Orth's fluid, sections were made from various regions from paraffin blocks and stained with hematoxylin and eosin, Van Gieson's, Mallory's and Giemsa's method. Levaditi's method for spirochetes was tried, but proved unsuccessful in all organs, due most likely to the unsuitable fixation.

When one examines the sections one is at once struck by the great number of Hassall bodies scattered not only throughout the medulla, but also in the cortex of the gland. The word "cortex," in fact, can hardly be used, as the reticular epithelium is in such preponderance over the small thymic lymphocytes that there is no sharp boundary as in the normal organ. Moreover, the perilobular connective tissue shows a marked fibrous increase, and throughout the parenchyma of the gland itself are broad areas which are almost entirely fibrous and even hyaline (Fig. 1).

In the upper part of the thymus are situated the cysts. The largest is about 3 mm. in diameter. Another is somewhat smaller, and two others consist of narrow slits about 0.5 to 1 mm. in breadth. The cysts are lined with a layer of epithelial cells which resemble somewhat in appearance the stratified squamous epithelium of the pharynx. In some places this layer shows local thickenings, and in these Hassall bodies are seen (Fig. 2). The larger cysts occupy almost an entire lobule of the gland and contain a granular detritus in which are a few lymphocytes and polymorphonuclear cells. The perilobular connective tissue is considerably thickened and forms a dense fibrous capsule around the cyst and its epithelial lining.

The local thickenings of the epithelium and their enclosed Hassall bodies furnish evidence as to the true nature of the epithelial lining. This is evidently simply the hypertrophied epithelial reticulum of the thymus, which by crowding together of its cells, along with the disappearance of the thymic lymphocytes, ultimately forms an almost solid layer of cells. The cyst, which is constantly increasing in size by a process to be described later, encroaches more and more on the lobule which contains it, so that in the end the thymus tissue consists merely of a thin layer of closely approximated reticular epithelial cells, with here and there a large remnant of the same cells, which may contain Hassall bodies, forming the local thickenings above described (Fig. 2).

The hypertrophy of the reticular epithelium which plays such an important part in this process is not limited to the neighborhood of the cysts, however. In every part of the organ the same appearance is seen. The lymphocytes are scarce, even entirely absent in some regions, and the tissue is composed of cells with a large amount of clear, light-staining protoplasm and a large, oval, vesicular nucleus. Their resemblance to the "epithelioid cells" of the granulomas is marked, and they have been given this name by many writers. Figure 3 shows the epithelial nature of the thymus tissue in the neighborhood of a Hassall body. The lymphocytes are almost entirely absent, in comparison with the large number seen in the normal gland.

Closely related to this hypertrophy of the reticular epithelium is the large number of Hassall bodies. These, as before stated, are not limited to the medulla of the gland, but are found scattered irregularly throughout the lobules, some lying at the very periphery. The large number is evidently constantly increasing, as on close examination the new development of these structures is easily studied. The manner of formation is identical with that described by Hammar[9] for their normal development. "The formation seems to begin by a cell of the reticulum—more rarely a pair of cells—increasing notably in

9. Hammar, cited from Wiesel, J.: Pathologie des Thymus, Ergebn. d. allg. Path. u. path. Anat., 1911, **15,** Part 2, p. 474.

size and assuming a spherical shape; when they reach the neighboring cells by this growth, these are compressed by the pressure produced by the growing cells and wrap themselves in layers around the central cells. Also, the peripheral cells soon become hypertrophied, by which process the formation grows and new cells are added to its periphery." These words of Hammar could not be improved on to describe the excessive development of Hassall bodies in this abnormal thymus.

A similar exaggeration of the normal changes of the Hassall bodies is seen in their further development. Just as the normal Hassall bodies degenerate, so the new ones rapidly undergo regressive changes, and here, as in their excessive development, the process proceeds more rapidly and beyond the limits seen in the normal. Almost as soon as the clumps of the hypertrophied reticular cells can be recognized as Hassall bodies, the central cells

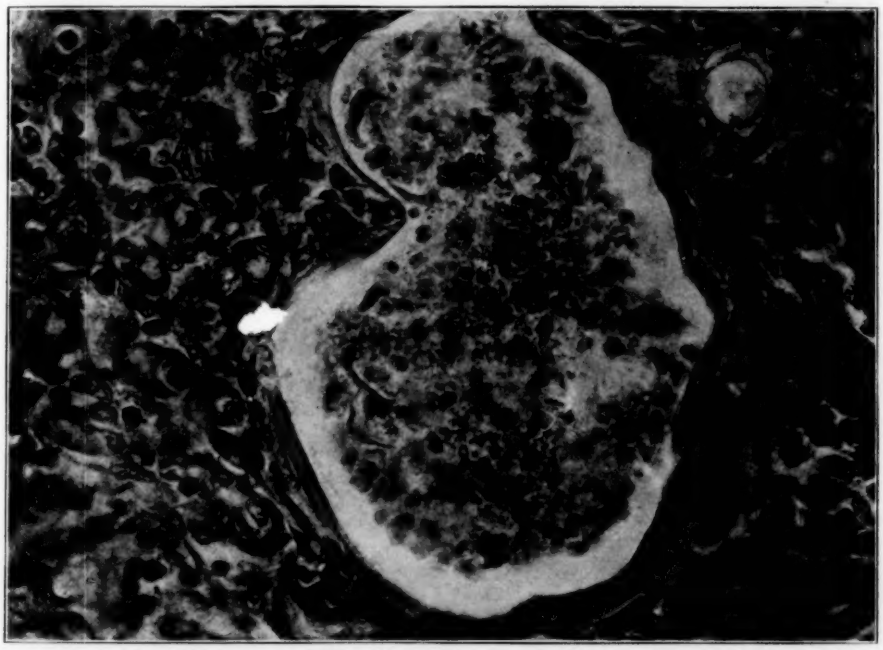

Fig. 3.—A dilated Hassall body about three times normal size. The character of the detritus and the epithelial lining of the structure are shown. Around the body the tissue is almost entirely epithelial, with a few lymphocytes. B. & L. Oc. 1. Obj. ⅙ in.

show necrotic changes. By the time the structure has reached the average size seen in the normal thymus, it consists of a single layer of flattened epithelium with a necrotic, granular center. But while in the normal degeneration of these bodies the process comes to a standstill at this point, in this case it continues, the surrounding reticular cells forming a new layer around the degenerating center. The Hassall body, which may now be termed a small cyst, increases in size, but its structure remains quite similar to that seen in the earlier stages of the process. Figure 3 shows such a cystic Hassall body with its thin lining of epithelial cells. It is about three times the size of the larger Hassall bodies seen in the normal thymus.

How far this cystic dilatation of the Hassall bodies might go is impossible to say, as another factor now comes into play. As has already been mentioned,

the number of Hassall bodies is greatly increased, so that they lie quite close together. When they reach a certain size in their dilatation, they come in contact with each other and then fuse by rupture of the thin epithelial wall which separates them; Figure 4 shows the process very clearly. A long sinuous cavity has been formed by the coalescence of the dilated Hassall bodies, while at the extremities of this cyst the process is still incomplete. If the process had gone on to completion, one sees that the lobule would have been entirely converted into a cyst similar to the large one heretofore described (Fig. 1), with the bordering remnants of the hypertrophied reticular epithelium forming the lining of the cavity. The clump of dilated Hassall bodies at the upper right hand corner of Figure 4 might furnish a local thickening of this lining, similar to that seen in Figure 1.

Fig. 4.—A narrow lobule of thymus tissue (dark) stretches across the lower part of the figure and connects two larger masses on each side. The lighter staining perilobular connective tissue is greatly thickened and shows an infiltration with round cells. The central part of the lobule has been transformed into a cavity, and at both extremities of this cavity the process can still be seen in progress, the dilated Hassall bodies fusing with each other. B. & L. Oc. 1. Obj. ⅔ in.

Before concluding the description of the pathologic findings, a word on the appearance of eosinophilic cells may be said. A large number of these were found scattered indiscriminately throughout the gland. There seemed to be no relation in their distribution to the degeneration of the Hassall bodies. These cells could be divided into two groups on the basis of their morphology. One type was the typical eosinophilic polymorphonuclear leukocyte of the circulating blood and that seen in the tissues in certain pathologic conditions. An equal number, however, were larger cells, with a large oval nucleus rich in

deeply staining chromatin, and with a large, irregular protoplasmic body filled with densely packed eosinophilic granules. These granules stained a more purplish-red than those of the typical eosinophilic polymorphonuclears. It seems probable that these are reticular epithelial cells, and that the granules represent phagocytosed granular material. It is interesting to note that the necrotic material of the Hassall bodies stains a similar color with Giemsa.

To sum up the pathologic findings of the case, we may say that we have to do with a thymus from a congenitally syphilitic infant in which cysts were present. These cysts had arisen by the cystic dilatation and coalescence of the Hassall bodies. Along with this degeneration of the Hassall bodies was an equally important hypertrophy of the reticular epithelium and new formation of concentric corpuscles, for without these progressive changes, it is doubtful if the cystic cavities could have arisen.

Which of the two processes is primary is difficult to say. One is apt to think in a general way of degeneration as the primary, with a compensatory hypertrophy. The presence of spirochetes (which unfortunately could not be demonstrated for technical reasons) might explain the rapid and early degeneration of lymphocytes and Hassall bodies, with a resulting release of "pressure" on the epithelium of the reticulum, and a hyperregeneration of the destroyed structures. The areas of fibrosis might also be explained in like manner. Whatever the relationship between the two processes, we can surely say that the cystic cavities in this case are not due to the developmental arrest, and have no connection with the original central cavity of the embryonic thymus. They have arisen from the cystic Hassall bodies in much the way described by Chiari and Schlesinger. As pointed out by Pappenheimer in his case, the large areas of fibrosis also show more than a developmental lack of differentiation.

How, then, are we to explain those cases in which a different origin of the cysts has been described? It would seem that in many of these the process had gone on to such a degree that the origin, which might well have been by the method here described, had been obscured. This would also explain the absence of Hassall bodies in these cases, as these structures tend to disappear with the increase in size and number of the cysts.

Another point demonstrated by this early case is the unity of the syphilitic processes in the thymus. Both Simmonds and Pappenheimer describe two types of lesions in such organs: one, the more rare, in which cysts are present, and those in which there is an epithelial hyperplasia with disappearance of the lymphocytes. Both types of lesion are found in the present case, and the former seems definitely dependent on the hyperregeneration of the degenerating Hassall bodies which goes hand in hand with the hypertrophy of the reticulum, for without a large number of these structures, fusion and the formation of large cysts would be impossible.

CONCLUSIONS

Syphilitic disease of the thymus in infants is manifested primarily by a degeneration of the lymphocytes and Hassall bodies, with a hypertrophy of the reticular epithelium and hyperregeneration of the concentric corpuscles. The process may give rise to the formation of cystic cavities by the dilatation and fusion of the degenerating Hassall bodies.

I wish to thank Dr. Ophüls for his kindness in reviewing this study.

CLINICAL DEPARTMENT

CONGENITAL ATRESIA OF THE RIGHT AURICULO-VENTRICULAR ORIFICE WITH COMPLETE ABSENCE OF TRICUSPID VALVES *

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Congenital atresia of the tricuspid orifice is a rare condition and to make this anomaly compatible with life, it becomes necessary that there be patent foramen ovale or at least an opening in the interauricular septum and that the two ventricles communicate. Associated with these, there may also be a patent ductus arteriosus. When the conditions mentioned above are the only anomalies, such a case is spoken of in the literature as an uncomplicated case. Of such we have been able to find records of eight cases to date. As complicated cases may be considered those in which there are further anomalies, such as transposition of vessels. The case which we have had under observation is as follows:

E. L., 8½ months old, was admitted to Michael Reese Hospital Nov. 5, 1914, and died Nov. 12, 1914, after having been under our observation for about four months.

The child had been ailing from birth, with marked difficulty in breathing and occasionally attacks of cyanosis. Five weeks before death the child had a much aggravated attack of dyspnea and very marked cyanosis, lips and face being very blue, the attack being accompanied by acute intestinal symptoms. This attack passed away and two weeks later the child awoke during the night, crying, as if in great agony; the eyes began to bulge, and he became very restless, his respirations being very short, labored, and superficial in character. The child became markedly cyanotic, the pulse being rapid and very weak and for several hours the mother feared that the child would die. The onset of this attack was sudden, without any fever, convulsions or vomiting. The attack passed off and during several days immediately before admission to the hospital the child had many other similar attacks. There was much loss of weight after the attacks became marked, but no fever throughout. The child suffered with bilateral otitis media, both ears discharging after the attack of pneumonia at 2 months of age. During the summer the child had several attacks of diarrhea, each of which lasted from seven to ten days.

The child was born at full term, the delivery being entirely normal without any attacks of asphyxia. The baby weighed 7½ pounds at birth. He was breast fed exclusively for about two months and artificially for the rest of his life.

The family history was negative, except that the mother had one miscarriage two years before, which, however, was due to an accident.

On admission the child weighed 8 pounds 3 ounces, the temperature was 95.6 F., pulse 112 and respirations 40 per minute.

The general appearance of the patient was that of an underdeveloped infant, with markedly protruding eyes, very marked cyanosis, rapid, irregular, labored breathing, rapid, irregular pulse, clubbed fingers and toes. The anterior fontanel was soft, large and slightly retracted. The posterior fontanel was closed. The suture lines about the occiput were palpable. The occiput was very prominent. The veins over the entire head were prominent and the pulse at times was very distinct about the head. The skin showed a marked sclerema and was of almost board-like consistency. The eyes were cyanotic, and there was marked exophthalmos, the pupils being equal in size and moderately dilated and reacting to light. Both ears were discharging a large quantity of very foul, thick, greenish-yellow pus. There was no apparent mastoid tenderness. The throat was negative. The lips were cyanotic, dry and covered with small scales, and the tongue was coated. No teeth had erupted. The neck was retracted and very rigid. All the vessels in the neck were greatly filled and pulsated. The venous pulsation was very marked. A marked in-drawing was seen in the suprasternal notch. The liver was palpable almost at the level of the umbilicus, having a hard, rounded edge. The spleen and kidneys were not palpable. The genitals showed slight cyanosis, no discharge. The extremities were markedly cold and cyanotic, the tips of fingers and ends of the toes clubbed and especially cyanotic. There was no marked tenderness and no other deformity. There was some rigidity of the spine, with marked retraction of the head, but otherwise the spine was negative. There was a slight Brudzinski, a suggestion of Kernig, no Babinski, no tache cerebrale and no clonus. The patellar reflexes were exaggerated.

The intercostal spaces were somewhat retracted and the veins over chest were dilated. The lung findings were negative. In the fifth interspace a diffuse apex beat could be seen. On percussion the boundary of the heart on the left side was found to be just at the nipple line, on the right side about 0.5 cm. externally from the right sternal border. The upper border was at the second rib. Over the base a long, loud systolic murmur was heard, which was thought to be best heard over the pulmonary region. No murmurs were heard at the apex.

Blood examination on the day of admission showed 85 per cent. hemoglobin, 4,500,000 erythrocytes, 12,700 leukocytes, the differential being 20 per cent. polymorphonuclear neutrophils, 60 per cent. small mononuclears, 13 per cent. large mononuclears and 7 per cent. transitionals.

From the foregoing findings a diagnosis was made of congenital heart disease, passive congestion of the liver and bilateral otitis media.

On the day of admission the child's temperature was subnormal (95.6 F.) and after that the temperature curve was irregular, rising in the first three days to 101.8 F. at 8 p. m. on the third day, then suddenly dropping to subnormal, 95.2 F., at midnight of the same day; then being slightly above the normal, it rises to 102.6 F. in the morning of the day of death, but falling to 97.5 F. shortly before death. Pulse-temperature and pulse-respiration ratios were not disturbed.

On the first day the child took nourishment poorly, retaining only about one half. It was losing weight continually, the last weighing before death showing 7 pounds 4 ounces as compared to 8 pounds 3 ounces on the day of admission. Especially during the attack of dyspnea and cyanosis the food was taken very poorly or sometimes not at all. On the day of death the child suffered with marked cyanosis, respirations being very labored, and it was unable to take any food. The ears continued to discharge pus. The child died eight days after admission to the hospital.

A roentgenogram of the heart (Fig. 1) shows a very broad shadow at the base, with a marked bulging in the region of the right auricle. A similar broadening is also seen in the region of the left auricle. The transverse

diameter of the shadow is also much greater than would be expected in an infant of this age. This broadening of the shadow involves both the right and the left sides of the heart. Compared with the necropsy findings, the broad basilar shadow was seen to be due to enlarged right and left auricles, and the broad transverse diameter of the lower part of the shadow in part to the large left auricle and in greater part to the large left ventricle.

At necropsy the organs were found to be normal, with the exception of mottling and congestion of the liver and marked abnormalities in the heart. The heart extended from the second to the seventh intercostal space. Practically the whole base of the heart was composed of the right auricle, the right ventricle being a small cavity which appeared almost as an appendage to the right auricle, and was located at the base of the heart about the level of the auriculoventricular septum, with its greatest diameter placed transversely and its cavity about the size of a large lima bean. The body of the heart was

Fig. 1.—Outline of heart, with broad shadow at the base and marked bulging in the region of the right auricle.

composed of the left ventricle, which was greatly hypertrophied. The left auricle was also greatly enlarged. The right auricle was prominent, immensely dilated and of a dark blue color. The foramen ovale was large and open. The tricuspid orifice and tricuspid valve were absent, there being nothing to mark the place where they should be. The interventricular septum was perforated by a small opening located at the upper part of the left ventricle, and this opening was about one sixteenth of an inch in diameter. The mitral orifice was dilated, being of such a size that a finger could be passed through easily and the mitral valve was very large, the papillary muscles being of exceptional size, and being attached obliquely rather than transversely as normally seen. The ductus arteriosus was rather small but patent. The aorta and pulmonary arteries were in practically normal relation, as were also the pulmonary veins

and vena cava, except as they were displaced at their origin due to the malposition of the various orifices of the heart. The pulmonary artery showed no stenosis, although as a whole it was considerably less in caliber than one would find in a normal heart. The pulmonary arteries were normal in structure although of smaller size than normal.

According to these findings the blood current in the heart was as follows: All venous blood went from the right auricle into the left auricle, thence to left ventricle, thence most of it went into the aorta and systemic arteries. A small percentage (possibly about 20 per cent.) went through the interventricular

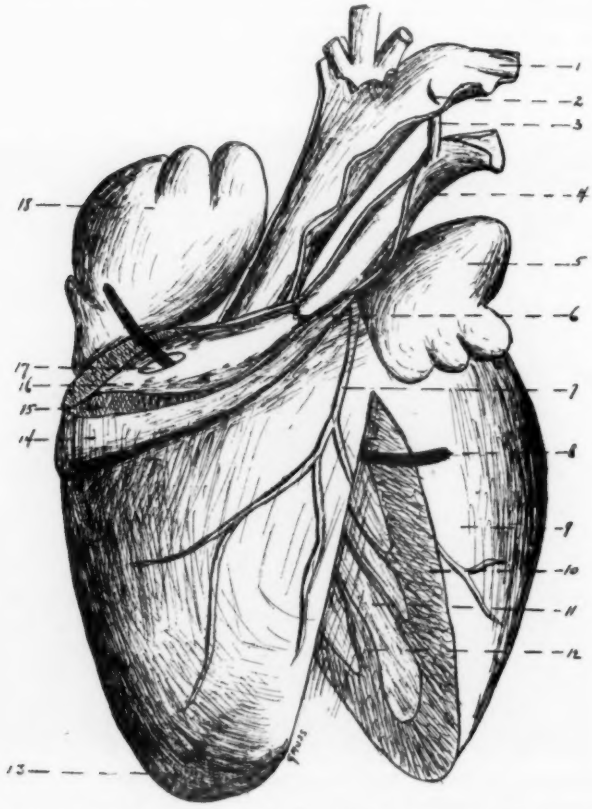

Fig. 2.—Anterior view of the heart, dissected: 1, aorta; 2, orifice of ductus arteriosus; 3, patent ductus arteriosus; 4, pulmonry artery; 5, left auricle; 6, pulmonary valves; 7, anterior coronary artery; 8, probe in interventricular opening; 9, left ventricle; 10, left wall; 11, left ventricular cavity; 12, papillary muscle to mitral valve; 13, apex of heart; 14, right ventricle; 15, right ventricular wall; 16, right ventricular cavity; 17, interventricular opening; 18, right auricle.

foramen into the right ventricle and thence into the pulmonary artery and lungs, and a very small percentage of this was shunted by the dulcus arteriosus into the aorta.

Summing up the case, we find that the chief abnormality was the tricuspid atresia, which, not admitting blood to the right ventricle, resulted in arrested

development. The atresia was partly compensated by an open foramen ovale, which, however, was not entirely sufficient and thus general venous congestion was produced. As less than one fourth of the blood reached the lungs by way of the abnormal interventricular opening, the blood was not sufficiently aerated, was abnormally rich in carbon dioxid and produced cyanosis. Thus the tricuspid atresia seems to have been the primary lesion, all the other abnormalities being somewhat of a compensatory character.

On the symptoms of attacks of cyanosis and dyspnea, clubbing of fingers and toes, venous congestion, enlargements of the heart and wide mediastinal shadow as seen by the roentgenogram (Fig. 1), and systolic murmur at the base, a diagnosis of congenital heart disease was made, the nature of the abnormality and full extent of the lesions remaining problematic until the necropsy was performed.

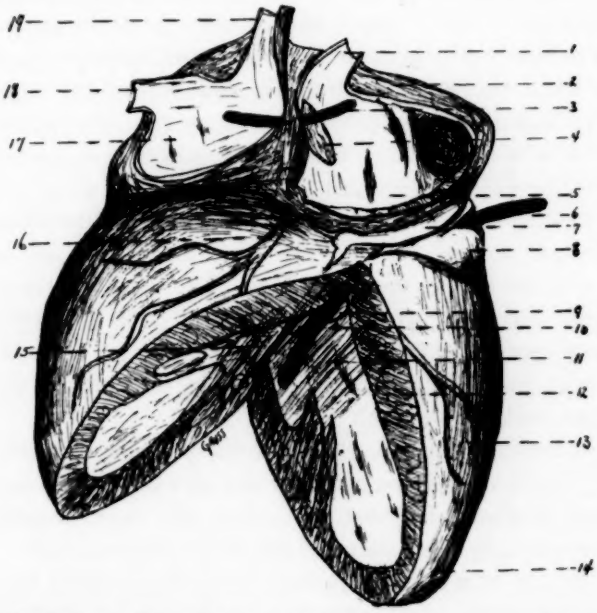

Fig. 3.—Posterior view of the heart, dissected: 1, superior vena cava; 2, right auricle; 3, probe in patent foramen ovale; 4, patent foramen ovale; 5, dependent portion of right auricle, showing no evidence of tricuspid valves; 6, probe in interventricular opening; 7, coronary sinus; 8, right ventricle; 9, interventricular opening; 10, entrance to aortic orifice; 11, left ventricular cavity; 12, left ventricular wall; 13, left ventricle; 14, apex of heart; 15, mitral valve; 16, posterior coronary artery; 17, left auricle; 18, pulmonary veins.

Congenital tricuspid atresia (aplasia ostii venosi dextri) is one of the rarest congenital anomalies of the heart. Rauchfuss[1] in his work on the diseases of the circulatory organs in children gives only five cases as found by him in the literature. The cases were those described by Kreysig, Vrolik, Nuhn, Valleix and Peacock. Vierordt[2] in 1901

1. Rauchfuss: Die Krankheiten der Kreislauforgane, Gerhardt's Handbuch d. Kinderkrankheiten, 1878, **4**.

2. Vierordt: Die angeborenen Herzkrankheiten, Nothnagel's spez. Path. u. Therap., Vienna, 1901, **15**.

adds to these five cases three more, those of Chapotot,[3] Gelpke[4] and Aschoff-Schreiber.[5] Kühne[6] describes two further cases of her own of tricuspid atresia. Wieland[7] describes one case of his own, which makes eleven cases in all.

In all the cases described there had been present, besides the tricuspid atresia, a defect of the septum and open foramen ovale. The ductus arteriosus was in some cases open, in others closed. In the cases of Kreysig,[8] Peacock and Gelpke there was found, besides atresia of the tricuspid, a transposition of the large vessels; in Klug's case a growing together of the two pulmonary valves, also narrowing of the pulmonary artery, otherwise described as normally large.

It is evident that one must separate complicated cases of heart anomalies from uncomplicated, simple and typical tricuspid atresia, as shown by Kühne in her work. As a simple tricuspid atresia may be regarded those cases in which there are septal defects and open foramen ovale, these being regarded as necessary accompaniments of the tricuspid atresia. While it is possible that they are direct adjustments to the tricuspid atresia, yet they are conditions which are absolutely necessary for the life of the individual. The cases of Kreysig, Peacock, Gelpke and Klug were complicated by other anomalies, which leaves seven uncomplicated cases, to which Wieland adds also Sieveking's[9] case as uncomplicated tricuspid atresia, thus making eight cases, our own case making the ninth.

In all its findings our case resembles these simple or uncomplicated cases of tricuspid atresia, the necropsy findings being also very similar. Antemortem diagnosis in those cases was also only congenital heart disease, the necropsy later showing the exact abnormalities.

As to the age at which the patients in these so-called cases of isolated tricuspid atresia died, according to Kühne all died during the first year of life, with one exception, Chapotot's girl, who reached the age of nearly 2 years. Our patient also died in the first year of life at the age of 8½ months. Other patients with tricuspid atresia, complicated with other heart anomalies, lived longer: Vrolik's patient nine

3. Chapotot: Lyon méd., 1889, **62,** 424.
4. Gelpke: Seltener Fall von angeborenem Herzfehler, Inauguraldissertation, Basel, 1883.
5. Aschoff-Schreiber: Deutsch. med. Wchnschr., 1901, Association Supplement, p. 63.
6. Kühne, M.: Ueber zwei Fälle kongenitaler Atresie des Ostium venosum dextrum, Jahrb. f. Kinderh., 1906.
7. Wieland: Zur Klinik und Morphologie der angeborenen Tricuspidalatresia, Jahrb. f. Kinderh., 1914, **79,** 320.
8. Kreysig: Krankheiten des Herzens, Berlin, 1817, **3,** 104.
9. Sieveking: Tr. Pathol. Soc., 1854, **5,** 97.

years, Favell's[10] ten years, Holmes'[11] twenty-one years, Gelpke's twenty-seven years, and in the last case published by the Basel Pathological Institute the patient lived fifty-three years.

The course and clinical symptomatology of congenital tricuspid atresia are those of a congenital pulmonary stenosis, with the distinction that in the formed one there is a hypertrophy of the left ventricle, while in the latter, a hypertrophy of the right ventricle. Furthermore, the systolic murmur heard in all cases is said to be more pronounced to the right of the sternum in tricuspid atresia, and to the left of the sternum in pulmonary stenosis. As in pulmonary stenosis, the children are affected by cyanosis and dyspnea. The heart pulsations are spread generally over the precordium.

Important in the diagnosis of tricuspid atresia is the hearing of loud systolic murmur, having its point of maximum intensity at the base of the heart (sternum), the intensity diminishing from that part. In pulmonary stenosis the murmur is loudest and heard best in the second left intercostal space. Murmurs in congenital anomalies of the heart are known for their constancy.

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10. Favell: Province méd., **3,** 440.
11. Holmes: Edinburgh Med. and Chir. Tr., 1824, **1,** 252.

PROGRESS IN PEDIATRICS

RECENT WORK IN ANATOMY, PHYSIOLOGY AND PATHOLOGY OF CHILDHOOD*

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ANATOMY

THE PARATHYROIDS

The relative position and histologic anatomy of the parathyroid glands, from early fetal life up to advanced age, have recently been studied by Thimm.[1] His material was quite varied: neck organs from over a hundred bodies, mostly adult; material from the eleventh and fifteenth year; some infants under 2 years of age (three prematurely born infants, sixth and seventh month); serial sections of three embryos of 3 cm. length, 5 weeks and 2½ months, respectively, and, finally, a variety of lower animals, laboratory animals, and others from zoological gardens. The work was done under the supervision of Professor Hansemann.

Thimm found the anatomic position of the superior pair of parathyroid bodies very constant. The inferior pair, on the contrary, are often pushed laterally, seldom up or down, by swelling of neighboring lymph glands, tumor formation, and the like.

In size the bodies measure 2 to 4 mm., in 1- to 2-year-old children, and are not yet flattened, oval or leaflike, as in the adult, but more globular in shape. In adults they are ellipsoid, leaflike, or very flat, and measure about 3 by 5 by 6 to 10 mm. Where they are as much as 12 mm. long, they are unusually narrow, for example, 12 by 3 mm.

The color of the parathyroid bodies varies considerably in microscopic preparations (Halsted technic). Characteristically, the parathyroid bodies take a reddish tone. Most commonly they take a lighter shade, one between this and yellow. In cachectic and anemic individuals the color becomes entirely yellow, and the whole parathyroid body closely resembles fat. Usually, however, the gland can be distinguished from fat in the neighborhood by the somewhat lighter color of the latter.

When a distinction can be made between the individual glands, the

* Submitted for publication Dec. 10, 1916.

1. Thimm, L.: Zur Kenntniss der Epithelkörper (Glandulae Parathyroidae), Arch. f. Kinderh., 1914, **63**, 321.

lower pair usually correspond in size. The upper pair tend to be smaller and more yellow, like adipose tissue. The lower stand out in sharper contrast with the surrounding tissue, and, when not in direct contact with the thymus gland, present a more typically elongated or oval form.

Thimm is impressed with the fact that the parathyroid bodies are found well preserved and strikingly constant and symmetrical in position, even in advanced age.

He found no true accessory thyroid glands (in human material). Projecting portions of the main glandular mass may be so cut as to present in sections the appearance of isolated bodies, but further study of the sections invariably showed that these were but part of a single glandular mass. Thimm did not find more than two parathyroid bodies on any one side, nor more than four in all. He is not familiar with the histologic picture of the "carotid glands."

The curvature of the neck region in embryonic life is associated with a certain amount of overriding of the branchial arches and clefts. This has some influence on the relative positions of the derivatives of the structures.

In the 3.5 cm. human embryo, Thimm found the two superior parathyroid bodies present in two fully symmetrical, clear-staining, round bodies lying on the posterior surface of the lateral margins of the developing thyroid. Immediately below each of these and somewhat laterally and ventrally, lay a larger, less globular, but otherwise entirely similar body, of like cell type, the inferior parathyroid of that side. Each of these bodies was continued distally, as a cell column with a more or less well-defined lumen which passed over medially into the thymus, the nuclei assuming the form characteristic of the thymus. These cell columns Thimm regards as the last remains of the cleft groove, the third medial branchial cleft, from a dorsal thickening of the wall of which arises the parathyroid, and from a ventral thickening, the thymus.

The relative position of the superior and inferior parathyroid bodies in the adult is already indicated in the 3.5 cm. embryo, the latter lying ventral and laterally to the former, though here still in actual contact with it. Through the relations of the lower mass to the thymus, the inferior parathyroid bodies are drawn downward as the thymus follows the heart in its descent and are pushed laterally as the thymus enlarges.

In the 5-weeks-old human embryo, the superior parathyroid bodies were found at the level of the thyroid isthmus, or slightly above it. The inferior pair lay below and somewhat ventrally to them and immediately adjacent to the thymus tissue. No distinct connection between the thymus and adjacent parathyroids could be demonstrated in this

instance. In the 2½ months fetus, only one parathyroid body was found on the left side, and it occupied an intermediate position. It could not be determined whether this represented the superior or the inferior parathyroid body.

According to Thimm, the vascular system can often be clearly distinguished in serial sections of uninjected tissues. He pictures the vascularization of the parathyroid bodies as follows: An arterial stem enters at the hilus and divides into a number of branches of equal size. These subdivide into smaller vessels, and eventually into a network of capillaries. Adjacent to these lie lymph spaces bathed with tissue juices. The veins arising from the capillary network proceed directly to definite centers, or to the hilus. Broad lymph spaces accompany them to the hilus, or, in peripheral regions, proceed to the capsular spaces and thence to the hilus. Any secretion probably occurs into the lymph spaces.

As regards the types of cells found in the parathyroid bodies, Thimm recognizes the four types described by Welch.[2] He finds, however, that the oxyphilic cells appear first after the twentieth year of life, and increase in number with age. They never at any time form a considerable proportion of the cells.

No undoubted secretory globules (*Tröpfchen*) were found in material from children under 2 years of age, nor, though the examination here was not so extensive, were any found in material from a boy 15 years of age. The tissues were stained with hematoxylin and eosin.

Staining tissues with sudan III revealed small and very fine fat droplets scattered over the entire section. Occasionally evidences of past hemorrhages (Erdheim) were found, and in one instance (tissues from an individual who died of chronic lead poisoning at an advanced age) there were found, in the oxyphilic cells, minute round golden droplets with a surrounding clear zone; these were thought to be altered blood pigment, and were present also in adjacent connective tissue.

THE TONSILS

Though possession of exact knowledge of the relation of the tonsils to the adjacent structures would seem to be a matter of some importance in operative procedures on them, G. Hudson Mackuen[3] has recently called attention to the common lack of knowledge regarding the nature of the so-called "capsule" of the faucial tonsils, and its relation to the intrapharyngeal fascia.

If the faucial tonsils possess a true capsule, removal of the tonsillar

2. Welch: Jour. Anat. and Physiol., 1898, **32,** 292.
3. Mackuen, G. Hudson: The Surgical Anatomy of the So-Called Capsule of the Faucial Tonsil, Laryngoscope, 1915, **25,** 685.

tissue and the subjacent capsule would seem to be the cleaner surgical procedure, and one that would prevent further growth of adenoid tissue in this location. If, however, the connective tissue lying immediately subjacent to the adenoid (tonsillar) tissue and closely attached to it is but part of the intrapharyngeal fascia, or aponeurosis, that encircles the pharynx, then to remove that portion of it which lies just behind the tonsil may be but to form a window in the sleeve of fascia that underlies the mucous membrane of the pharynx, and interposes a barrier between this and the loose connective tissues of the neck and mediastinum. Such a window or defect might be conceived of as permitting ready entrance into the body of bacteria and the products of inflammation.

Mackuen quotes Dr. D. R. Patterson, special throat surgeon to the King Edward Hospital, Cardiff, as one who has made careful study of the anatomy of the faucial region, both in man and the lower animals. Patterson says the so-called capsule of the tonsil is merely a portion of the intrapharyngeal fascia or aponeurosis, having its upper attachment at the base of the skull and extending down into the region of the esophagus. In confirmation of this belief he quotes freely from the English and French schools of anatomy. This view Mackuen endorses on clinical grounds.

Adenoid tissue is found everywhere in the mucous membrane that clothes the fascial layer surrounding the pharynx. At the side of the future faucial tonsils this adenoid tissue undergoes a relatively great development, or hypertrophy. That in the vault of the pharynx undergoes a lesser development; when excessive or obstructive it is spoken of as an adenoid growth or vegetation. Mackuen says:

> In the course of its development in the embryo and during infancy, the tonsil appears to appropriate a portion of the connective tissue and musculofibrous tissue with which it is in juxtaposition, and finally, in adult life, it becomes firmly attached to the membrane, to which has been given the name intrapharyngeal aponeurosis, and a section of which seems to constitute the so-called capsule of the tonsil.

The closeness of the union increases with age, and is the result of physiologic as well as pathologic processes. The blood supply of the tonsil, passing through the intrapharyngeal aponeurosis, tends to bring about a still firmer union between the tonsil and its capsule. In very young children, the mass of adenoid tissue (tonsil) may at times be peeled out of its bed or pocket with very little connective tissue attached to its surface. This may be so scanty and so delicate as to suggest that it is merely a compressed portion of the subareolar connective tissue in which the adenoid (tonsillar) tissue happens to be embedded. With increasing age, closer and closer union takes place between the tonsil and the aponeurotic fascia. The tonsil seems to

grow fast to the membrane, and more and more of it is torn away in attempts at removal. The occurrence of pathologic processes favors this closer union.

PHYSIOLOGY

BODILY DEVELOPMENT

T. I. Grover[4] finds that the head and breast measurements of a child stand in closer relation to weight than to age; that the length of the arms and legs is in direct relation to the height; and that, in general, one can judge of a child's development better by his weight and growth than by his age.

Max Guttmann[5] gives statistics from individuals measured on the day of birth and thereafter, with great exactness, through a series of years, even up to the age of 28. The details are too numerous for abstracting.

ELECTRICAL REACTIONS OF NORMAL CHILDREN

That it is possible to detect certain states of abnormal excitability of the nervous system by the determination of what is called the electrical excitability of a typical peripheral nerve has been held by pediatrists for many years. The degree of electrical excitability is expressed in terms of the number of milliamperes of galvanic current required to provoke minimal contractions in the muscles supplied by, for example, the ulnar or the peroneal (external popliteal) nerve. In typical instances of hyperexcitability, contractions may be obtained in each phase of galvanic stimulation; that is, there is a contraction of the muscles with making and with breaking both the cathodal and the anodal (or reversed) current. In most normal individuals, however, the muscles contract in only two or more of the four phases, unless excessively strong currents are employed. The amounts of currents required in each instance to produce minimal contractions are called the "electrical values" of the individual.

The most characteristic form of electrical hyperexcitability of the nerves is seen in the condition known as tetany. Erb called attention to the presence of this increased electrical excitability in adult patients suffering from tetany, and later workers showed that it is found also in cases of the disease in infants and children. At the same time Erb advanced the hypothesis that there occurs a latent form of the disease in which the other characteristic phenomena or symptoms of tetany may be in abeyance and a diagnosis of the presence of disease possible only through a demonstration of abnormal electrical values.

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4. Grover, T. I.: Some Measurements of Normal Children, Arch. Pediat., 1915, **32,** 472.

5. Guttmann, Max: Einige Beispiele individueller körperlicher Entwicklung, Ztschr. f. Kinderh., 1915, **13,** 248.

Stintzing, in 1886, examined a large number of persons of various ages with the faradic current and published tables giving the mean value for each of the peripheral nerves and the normal range of variation therefrom that may be expected. These Stintzing tables are made the basis of clinical neurologic investigation, being accepted as the standard of normality. Stintzing recorded also the cathodal closing values, but he did not investigate the values for the other phases of galvanic electrical stimulation. It is the determination of these other values that has proved most serviceable in the study of tetany.

Escherich, Thiemich and Mann, and finally von Pirquet, studied the galvanic electrical reactions as they occur in infants and very young children. The standards established by these authors for infants and young children have been utilized by other workers for older children, even those approaching puberty. It has been assumed that the standards for electrical reaction in infancy were applicable, without modification, to children of 5, 10, or more years of age, and not a little confusion has resulted.

It has become evident that the galvanic electrical standards of infancy are not applicable without modification to older children; and that there is a change in the normal galvanic electrical values that is more or less coincident with change in age.

Holmes[6] has recently examined the galvanic electrical values in a large number of children in each year of life from birth to puberty. The results of his study have been summarized as follows:

1. There is a gradual transition from the high electrical values of early infancy to the relatively low values of adult life.

2. Values below 3 milliampères, other than cathodal closing values, are rare in the first six months of life, but appear with increasing frequency thereafter.

3. Cathodal opening contractions with a current of less strength than 5 milliampères are of infrequent appearance in normal children of any age; they probably do not occur in normal children under 5 years of age. The same may be said of cathodal closing tetanus.

4. The presence of anodal opening contractions with a current less than that causing anodal closing contractions and under 5 milliampères (anodal hyperexcitability), occurs with gradually increasing frequency from the first half year of life upward, reaching its maximum frequency in children of 6 or 7 years.

The actual figures obtained are given by Holmes in two tables. The first table gives the *average* values found in normal children in each year of life. Not all children present the average or mean value. Stintzing showed that in adults quite a wide range of normal variation might be expected; for example, the cathodal closing value may be 0.2 to 2.0 milliamperes for the peroneal nerve at Erb's point, the

6. Holmes, J. B.: The Reliability of the Electrical Diagnosis of Tetany, etc., Am. Jour. Dis. Child., 1916, **12**, 1.

average being 1.0 milliampere. A similar range of normal variation is found in infants and children. The extremes found in examining the same apparently normal children are given in the second table.

Taken together the two tables afford a standard or norm for use in examination of the galvanic electrical excitability of the nerves of infants and young children, and are thus comparable to the Stintzing tables for faradic excitability.

From the point of view of pure physiology it is desirable that the investigation be extended into adult life. The practical application of the tables, however, is to the study of conditions of latent and active tetany in infants and young children, and in this the tables are a much needed extension of the work of the authors before mentioned.

THE BLOOD

Kunckel[7] has studied the hemoglobin and cellular content of the blood of prematurely born, but otherwise healthy, infants during the early months of life. His material consisted of sixty premature infants, seven twins and seven "debile" infants. It is not certain that the last mentioned fourteen were prematurely born. Most of the children came under observation in the second or third week of life. The youngest received breast milk, others were given milk modifications and food adapted to their age. The average weight of those under two months of age was 1,900 gm. The average monthly gain in weight was somewhat over half the normal. The infants remained unusually free from coryza or other acute infections. The hemoglobin content of the blood was determined with the Sahli hemoglobinometer.

As a normal standard for comparison, Kunckel used the figures obtained by J. Levy (Detroit) from other children in the asylums of Berlin, stating, however, that Levy's figures may be too low for normal infants in general, owing to the social status of the material from which they were obtained. Levy's figures for the average hemoglobin content of the blood at various ages are: in the second month, 70 per cent.; in the third month, 65 per cent.; in later months, 50 to 60 per cent.

Kunckel found that the hemoglobin content of the blood was uniformly high (average 104.8) in those premature infants examined in the first two weeks of life; and that it then declined more rapidly than in normal full-term infants, and reached a lower level. The actual figures, average values, are: in the second month, 55.2 per cent.; in the third month, 46.5 per cent.; in the fourth month, 49.6 per cent.; in the fifth month, 52 per cent.

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7. Kunckel, D.: Zur Kenntnis der Blutveränderungen bei Frühgeburten und debilen Kindern, Ztschr. f. Kinderh., Orig., 1916, **13,** 101.

These figures were further established by isolated observations on other healthy premature infants, the additional observations yielding results similar to the above.

The red cell count in contrast with the hemoglobin varied but little from the normal. The average for the first year, exclusive of the first month, was 4,085,000. Anisocytosis and poikilocytosis were often seen, but no other abnormalities.

The white cell count differed from the normal in that, instead of the usual 12,000 to 13,000 cells per cubic millimeter, the average between the second and the sixth month was 7,800. The count rose, as in other infants, on the appearance of furunculosis or other inflammatory processes. The morphology of the white cells was essentially normal.

In discussing possible etiologic factors for the striking relative anemia of the prematurely born, Kunckel mentions Hagouneng's observation that the content of the fetus in iron is twice as great during the last third of pregnancy as during the first two thirds. He adds, however, that this finding must be qualified by Philippson's observation that the size of the supply of iron varies considerably in fetuses in the same month of intra-uterine life.

Kunckel was not able to show that the weight of the premature infants in his material and their later hemoglobin percentages stood in any constant relation. He gives as one instance the case of twins, admitted on the eleventh day after birth, and showing approximately the same weight and erythrocyte count, who yet differed widely in their hemoglobin percentage (120 versus 80), and maintained this difference (85 versus 55, in the beginning of the second month, and 68 versus 45 at the end of the second month). Differences in tying off the cord, and the like, could hardly explain such findings.

Whatever the cause of the primary lack of iron hemoglobin may be, the condition appears to pass slowly over into the normal during the second half year. (Kunckel's observations on this point seem insufficient.) In no case did a severe anemia develop. Clinically, open air treatment led to a marked improvement in the hemoglobin percentage. The effect seemed to be due to the improvement in the general metabolism of the body, in which the iron metabolism shared.

LEUKOCYTOSIS OF DIGESTION

A. Graeme Mitchell[8] examined fifty bottle-fed infants for the occurrence of a leukocytosis during digestion. He made over 700 blood counts. He finds that bottle-fed babies do not constantly show a digestive leukocytosis; in fact, the majority show a smaller number of leu-

8. Mitchell, A. Graeme: Leukocyte Counts During Digestion in Bottle-Fed Infants, Am. Jour. Dis. Child., 1915, **9**, 358.

kocytes in the superficial blood after taking food than before. This decrease becomes greatest from one to two and a half hours after feeding and then becomes less marked. When a rise does occur it appears most frequently soon after feeding and begins to decline in a half hour. There seems to be as yet no adequate explanation for the increase or decrease.

A careful review of the literature on the subject accompanies Mitchell's report. Most textbooks speak of a physiologic leukocytosis. Some standard works on pediatrics state that this leukocytosis is more pronounced in children. The majority of workers, however, hold that digestive leukocytosis is inconstant in both adults and babies.

NUTRITION

The exigencies of wartime in the central empires promise to furnish us with many practical studies in dietetics. One of the first of these comes from von Pirquet. He urges the use of increased amounts of sugar in wartime, because of the relative cheapness of this article of diet. He states that 50 per cent. of the total calories in the infant's diet may be given in this form and that older children may be given amounts up to 300 gm. daily. It is necessary in older children to increase the amount very gradually, else diminution of appetite, nausea or vomiting are produced. With this increased amount of sugar must be given much albumin (skim-milk, cheese, legumes, eggs, meat, etc.), otherwise there occurs no corresponding gain in weight.

In Austria, in 1915, the cost of 100 gm. of sugar, as compared with its nutritional equivalent in milk (600 gm.), was as ten to eighteen. (In this connection it may be mentioned that the per capita consumption of sugar in America is said to be much in excess of that of other nations.)

GASTRIC DIGESTION

Two studies on the gastric digestion of infants are reported by Finzio;[9] one on the occurrence of free hydrochloric acid in the gastric contents of infants, and another on the power of the gastric secretion in infancy to digest casein.

Finzio finds that the amount of free hydrochloric acid in the stomach content of infants is closely dependent on the milk diet. (In adults free hydrochloric acid may be lacking in the gastric contents after a milk meal or diet.) In adding progressively increasing quantities of a normal solution of hydrochloric acid to mixtures of mothers' milk and pepsin, he finds that digestion occurs in the presence of a deficit of "free" hydrochloric acid (0.1168 gm. HCl is bound by 100 c.c.

9. Finzio, G.: Valore dell' acido cloridrico libero nel contenuto gastrico del lattante, La Pediatra, 1915, **23**, 168.

of mothers' milk), but that it increases gradually as the deficit in "free" HCl is overcome. Similar studies with cow's milk yielded like results. Finzio concludes, therefore, that in infancy peptic digestion and splitting of albumin takes place in the absence of "free" HCl, and that "combined" HCl must play a part in gastric digestion.

Finzio[10] has studied also the peptic digestive capacity of the gastric content of infants after a fictitious meal; that is, after sucking on a dry or nonlactating breast, and found in all cases that the after content of the stomach digested casein. When, however, the infants were given an actual nursing of milk, the gastric contents withdrawn a half hour after nursing showed no power to digest casein. When the fluid was withdrawn one hour after nursing, that from five out of ten cases digested casein, and at one and a half hours, that from nine did so.

MISCELLANEOUS

A number of writers have reported studies on the content of the blood of infants and children in uric acid, sugar, lipase, epinephrin, and other substances. E. Liefmann[11] has studied the uric acid content of children's blood. It was quite recently a debated question whether uric acid was present in the blood of healthy adults. With the introduction of newer methods of examination it has been found that the blood of healthy adults always contains a trace of uric acid. Bass and Wichowsky,[12] using a modified Ludwig-Salkowski method, found the blood of normal adults on a purin-free diet contains 1 to 2 mg. of uric acid per 100 c.c. of blood. Other workers, using colorimetric methods, have confirmed these results. When the diet contains purins, the uric acid level may rise normally to 3 mg. Occasionally the blood of apparently healthy individuals yields values that exceed the normal. In gouty individuals the content of the blood in uric acid rises to 5 to 6 mg. No studies appear to have been previously made on the blood of infants and children.

Liefmann employed an Autenrieth-Konigsberger colorimeter. His study was undertaken primarily to determine whether children with the symptoms of the exudative diathesis (Czerny) differ from normal children in the uric acid content of their blood. He examined six normal infants and four children (ages 14 months, 2½ years, 8 and 13 years). The infants were receiving a purely milk diet.

The blood of infants was found to contain 1.3 to 1.7 mg. of uric acid of 100 c.c. of blood. In the older children the values rose slowly

10. Finzio, G.: Sulla digestione della caseina nello stomaco dei lattanti, La Pediatria, 1915, **23,** 95.

11. Liefmann, E.: Ueber den Harnsäuregehalt des Kindlichen Blutes, Ztschr. f. Kinderh., 1915, **12,** 227.

12. Bass and Wichowsky: Wien. klin. Wchnschr., 1912, **25,** 1863.

(1.7, 1.8, 2.0 and 3.7 on mixed diet, respectively), until they reached the normal values for adults on mixed diet, 3.8 to 4.6 (Steinitz). Two nursing women examined showed no increase of uric acid content — 2.0 and 3.8.

The addition of thymus broth to the diet of milk-fed infants caused a prompt rise in the uric acid content of the blood, and the higher value diminished gradually after a return to a purin-free diet. Administration of atophan, ¼ gm., to infants with a normal concentration of uric acid in their blood caused a prompt reduction of this amount (to a trace), and the effect persisted fifty or more hours. Administration of "protojuret" caused, on the other hand, an increased concentration of uric acid. The occurrence of leukocytosis from any cause had a similar effect. Liefmann was unable to find any evidence of a relation between the so-called exudative diathesis and the uric acid (rheumatic) diathesis.

Heller[13] has investigated anew the sugar content of the blood of newly born and premature infants. Goetzky, Bang, and Windelöw and Mogwitz concluded that the blood sugar of nurslings shows the same normal values and variations as that of adults. Heller studied the matter with reference to the age, birth weight, and food intake of infants. The physiology of the newly born presents so many variations from that of older children and adults that certain differences in the sugar content of the blood might have been anticipated. Heller's studies on twelve full-term newly born infants and three premature infants show that no difference exists. He employed Bang's method of estimating the sugar content of the blood.

Goetzky[14] employed Bang's micromethod on 100 normal infants and young children. He found the average percentage of sugar in the blood of twenty-three children between the ages of 2 and 12 years to be 0.102, the extremes being 0.087 and 0.118. More recently Bass,[15] in the examination of the blood content of twenty-six normal children, ranging in age from 2 to 14 years, found an average of 0.089. He employed the Benedict-Lewis method and examined the blood from two and a half to three hours after breakfast. He found that neither age nor sex seemed to influence the sugar content.

Heller concluded that the reduction value of the blood of normal newly born and premature infants lies within the same range of physiologic variation as those of older nurslings and adults. Also that the

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13. Heller, Fritz: Der Blutzuckergehalt bei neugeborenen und frühgeborenen Kinder, Ztschr. f. Kinderh., Orig., 1915, **13,** 129.

14. Goetzky, F.: Der Physiologische Blutzuckergehalt beim Kinde nach der Mikromethode von Bang, Ztschr. f. Kinderh., 1913, **9,** 44.

15. Bass, Murray H.: The Sugar Content in the Blood in Childhood, Am. Jour. Dis. Child., 1915, **9,** 61.

nature of the food (colostrum, breastmilk, and cow's milk in one-third dilution) has no noteworthy influence on it.

Zamorani[15a] studied the contents of the children's blood in lipase. He employed the method of Rona and Michaelis (tributyrin) and determined the content in lipase of ninety-two specimens of blood from sixty-four children of various ages, and five adults. He used 0.25 and 0.5 c.c. of serum and examined it twelve to twenty-four hours after its withdrawal. Control studies showed that the presence or absence of hemolysis had no appreciable effect on the lipolysis. Zamorani found that while the content of the blood in lipase showed individual variations, there was no noticeable difference between specimens from normal nurslings, other children and adults. No specimen was entirely lacking in lipase.

While changes in the general bodily condition of a patient may, in some instances, be accompanied by a rise or fall in the content of the blood in lipase, there are no changes that are constant or that are characteristic of any particular disease. No variations from the normal were found in certain cases of tuberculous meningitis, or in children with acetonuria. It seems that disturbances of the fat metabolism, in contrast with those of the sugar metabolism, do not lead to excretion of the fat as such, though in some conditions the fat is not fully oxidized and appears in the urine as ketones. Zamorani opposes the view of Mellis-Schirm that in diseased conditions of the lymphatic system one may draw prognostic inferences from the content of the blood in lipase; and also the contention of Samelsohn that diminished fat splitting power of the blood of atrophic infants is a cause of the disease. It appears to him but a part of a general disturbance of the body.

S. Cannata[16] studied the occurrence of epinephrin in the blood of the newly born. He examined the blood of thirty-one infants, 3 hours to 6 days old, and employed Spolverini's modification of Ehrmann's method of detecting the presence of epinephrin. This method utilizes the iris of an isolated frog's eye, and is thought to detect epinephrin in dilutions of 1:20,000,000. Cannata found that the content of epinephrin in the blood of the newly born is so little that it is not detected by this test. This would correspond to the anatomy of the suprarenal gland in infancy, the cortex being well developed, the medulla scanty.

Schlutz and Pettibone[17] have made quantitative determinations of

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15a. Zamorani, V.: Sul contenuto in lipasi del sangue nell'eta infantile, La Pediatria, 1915, **23,** 401.

16. Cannata, S.: Sulla presenza di adrenalina nel sangue del neonato, La Pediatria, 1915, **23,** 244.

17. Schlutz, F. W., and Pettibone, C. J. V.: Quantitative Determinations of Nonprotein Nitrogen in the Blood of the New-Born, Am. Jour. Dis. Child., 1915, **10,** 206.

the nonprotein nitrogen in the blood of the newly born. Previous studies appear to have been confined to the blood of human adults and lower animals. Schlutz and Pettibone studied the conditions in a series of twenty-six infants varying in age from a half hour to 10 days. The total nitrogen, urea, ammonia, and amino-acid nitrogen of the blood were determined quantitatively. By nonprotein nitrogen is meant the nitrogen that is not precipitated by methyl alcohol and zinc chlorid (Folin's method). The source of the nonprotein nitrogen is almost entirely from the proteins ingested by the organism. The recent work of Folin and Van Slyke, and others, seems to indicate that ingested proteins are completely hydrolyzed in the digestive tract, and that most of their amino-acids are thus set free and are absorbed into the blood stream unchanged and thence taken up by the tissues.

Older methods showed that 100 c.c. of normal adult human blood contained as a maximum 50 to 70 mg. of nonprotein nitrogen. Newer methods show lower maximum figures. Folin and Denis[18] report a maximum of 22 mg. per 100 c.c. of blood. Of this the larger part is urea nitrogen — 11 to 13 mg. The percentage of both is at any given time higher in the portal blood than in the general systemic blood.

Schlutz and Pettibone find that the total nonprotein nitrogen per 100 c.c. of infants systemic blood is approximately the same as in the adult. Also that the age and weight of the infant and the period after feeding have no bearing on the total. The percentage of urea nitrogen is uniformly high and averages about 50 per cent. of total nitrogen.

The probable source of the amino-acids in the blood of the infant just born, or before the first feeding, lies in the placental circulation.

Tileston and Comfort[19] made a similar study on children suffering from pathologic conditions. Because of finding considerable variations when the specimens were taken just before the noon meal, they were led to take the blood, in the case of children over 2 years of age, before breakfast, after a fast of twelve hours or more. In the two normal cases studied in this manner there were 24.4 and 26 mg. of nitrogen, and 9.8 and 10.9 mg. of urea nitrogen, respectively. In children who are acutely ill and taking in consequence less than the accustomed amount of food, they found the blood might be taken at any time without the liability of error.

Fenger[20] and Pellegrini[21] studied the iodin content of the thyroid in

18. Folin and Denis: On Uric Acid Urea and Total Nonprotein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, **14,** 29.

19. Tileston and Comfort, C. W.: The Total Nonprotein Nitrogen and the Urea of the Blood, and the Phenolsulphonephthalein Excretion of Children, Am. Jour. Dis. Child., 1915, **10,** 278.

20. Fenger, F.: On the Presence of Iodin in the Human Fetal Thyroid Gland, Jour. Biol. Chem., 1915, **15,** 695.

21. Pellegrini, R.: Sul contenuto in iodio delle ghiandole tiroidi dei feti, dei neonati e dei bambini, Riv. di Clin. Pediat., 1915, **13,** 195; abstr., Jahrb. f. Kinderh., 1915, **32,** 174.

the young. Pellegrini found that iodin was present in about two thirds of the twenty-three cases examined by him; that the age had no effect on the quantity; and that iodin might be absent in large glands and met with in small ones.

Sedgwick[22] examined anew the question of oxalic acid excretion in the urine of children. Little work has been done on this. Aron and Franz concluded that the urine of infants contains small amounts of oxalic acid almost without exception. This was true even when an oxalic-acid-free diet was given. The addition of sugar, dextrimaltose or starchy matter to the diet was followed by a somewhat higher excretion. Sedgwick used the Albahary method of determining oxalic acid. He finds that newly born infants excrete oxalic acid in the urine in varying amounts up to 9 mg. per day, and that older children excrete considerable quantities. If the usual figures given for the excretion of oxalic acid in adults — 15 to 20 mg. (Neuberg) — are accepted, the excretion in children is relatively, and at times absolutely, higher.

Taylor[23] made an experimental investigation of the occurrence of creatin in the urine of children. Some years ago W. C. Rose noted the constant occurrence of creatin in the urine of children until about the age of puberty. This observation was later verified by Folin and others. The closely related compound ceratinin appears normally and constantly in human urine; creatin appears in the urine of adults in various forms of carbohydrate starvation and in severe forms of diabetes. It has been suggested that its appearance in the urine of childhood is due to a relative deficiency of carbohydrate in the diet. Taylor, however, finds that creatin continues to appear in the urine of children in spite of a high intake of carbohydrate. The sum of the creatin plus the creatinin in the urine of children compares approximately with the sum of the two constituents in the adult when due allowance is made for the weights of the individuals and the probable amounts of muscular tissues. These findings may reasonably be ascribed to an incomplete conversion of creatin into creatinin by the developing organism.

Veeder and Johnston[24] have examined the urine of twenty-one normal children for the presence of ketones and betahydroxybutyric acid. The results were so consistent that it seemed unnecessary to examine a larger number. The children ranged in age from 2 months to 12 years, and were receiving a standard diet of sufficient caloric value to cover the needs of children at light work or play. They were

22. Sedgwick, J. P.: Oxalic Acid Excretion in the Urine of Children, Am. Jour. Dis. Child., 1915, **10,** 414.

23. Taylor, A. E.: On Creatinuria, Jour. Biol. Chem., 1915, **21,** 663.

24. Veeder, B. S., and Johnston, M. R.: Presence of Ketones and Betahydroxybutyric Acid in the Urine of Normal Children, Am. Jour. Dis. Child., 1916, **11,** 291.

in bed, were afebrile, and had been on a standard diet for several days before the twenty-four hour specimen of urine was collected for examination. The methods of Schaffer and Messinger were used.

When the caloric values of these children were fully covered by the diet, small amounts of ketones and betahydroxybutyric acid were always found. The amount was small and varied from 20 to 100 mg. in terms of acetone in twenty-four hours, the amount excreted being 50 to 80 mg. As a rule, the amount of betahydroxybutyric acid was somewhat greater than the amount of other ketones, but this did not always hold true. The age, sex and body weight of the child had apparently no effect on the amount excreted. It would seem thus that the large amounts of acetone bodies that appear in the urine in febrile conditions and in restricted diets represent an increased excretion of substances normally present, rather than the appearance of abnormal substances.

THE INITIAL LOSS OF WEIGHT IN THE NEWLY BORN

The analysis of this phenomon by Benestad has recently been reviewed in this journal. Benestad viewed the initial loss of weight in the newly born as a physiologic condition, and spoke of the failure of all efforts to prevent the loss, or even to appreciably diminish it, by supplying newly born infants with milk from wetnurses whose children are but a few days older than the patient, as seeming to indicate a functional inability to utilize milk during the first days of life, even in a mature infant. Altherr's work seemed to show that forcing food at this time might even delay the normal recovery of the birth weight. Another attempt to prevent this initial loss of weight is now reported.

B. Schick[25] of von Pirquet's clinic has attempted to prevent the usual (physiologic) loss of weight in twelve infants. He states that there are exceptional infants who do not show this usual early loss of weight, and that there are well-established observations that subsequent children show less rapid and less prolonged initial loss of weight than first-born children. This is attributed to an earlier onset of the breast secretion in the multiparous breast. Early and more frequent application of the child to the breast is also said to be helpful. Recent studies by Jaschke and V. Reuss, embodying many cases, are cited as showing that the giving of indifferent fluids, or of woman's milk, may lessen the loss.

Schick attempts to prevent the loss entirely. He assumes that the initial loss of weight is due to insufficient supply of food, and that even where an abundant supply is at hand, the newly born infant can-

25. Schick, B.: Zur Frage der physiologischer Körpergewichtsabnahme des Neugeborenen, Ztschr. f. Kinderh., Orig., 1916, **13,** 257.

not avail himself of it, because of his inability to nurse properly — the infant is not born with a *fully* developed ability to nurse, he must *learn* to nurse; this he usually does in a few days. In the meantime Schick attempts to give a total amount of nourishment that will approximate the infant's needs, as computed from what is known of the needs of infants of greater age.

The optimum amount of (breast) milk for an infant from the second to the ninth month of his life, is, according to von Pirquet, 15 per cent. of the body weight, and the minimum, or mere maintenance ration, is 10 per cent. of the body weight. This 10 per cent. Schick attempted to give each infant during every twenty-four hours. In calculating the amount to be supplied, he allowed for the greater calorific value of mother's milk during the first week of nursing, as compared with later production. Only after the third day of life was the total amount of food received by the infant, breast feeding plus forced feeding, allowed to approach 15 per cent. of the body weight.

By this procedure Schick was able to prevent the initial or physiologic loss of weight in all cases. The infants are said to have held their weight, or gained slowly, during the first two or three days, during which time they were giving off their "dead ballast," meconium, swallowed amniotic fluid, etc., and then to have gained rapidly and well. During the first hours, vomiting of the ingested amniotic fluid disturbed the process of forced feeding in some instances — this vomiting may occur whether fluid be forced or not — but this soon ceased under continuance of the forced feeding. No injury to the children of any kind was discernible.

The practical difficulty of Schick's procedure lies, first, in the time required for such frequent forced feedings as he thought necessary — they were given every hour or so because of the large amount of fluid to be ingested during twenty-four hours — and second, in the difficulty in procuring sufficient mother's milk from women whose children are not more than 1 week old. From a purely theoretical point of view the work is of much interest.

BREAST SECRETION AND GENITAL BLEEDING IN THE NEWLY BORN

The occurrence of transitory swelling of the breast and the appearance of a mammary secretion (witch's milk) in the newly born has been known from the earliest times. The occurrence of the more infrequent phenomenon of genital bleeding in the newly born female infants has been known for a century or more. It has recently attracted scientific attention anew. Von Zappert[26] (1903) first

26. Von Zappert: Ueber Genitalblutung neugeborener Mädchen, Wien. med. Wchnschr., 1903, **53**, 1478.

described in a precise manner the pathologic anatomy of the uterus in such a case. Halban[27] extended these studies in the next year.

Clinically, the phenomenon seems to occur in 0.12 to 2.5 per cent. of all newly born female infants; histologic examination of the uterus, in a limited number of infants, shows that it appears in a much higher percentage of 8.3 to 38 per cent.

Zacharias[28] has recently examined 400 newly born female infants in Professor Zweifel's clinic. He found that genital bleeding occurred in 2½ per cent. of these infants. The bleeding occurs most frequently in large, heavy, full-term infants. It is not more common in first children than in later ones. Commonly the bleeding occurs drop by drop. It may be so slight as readily to escape notice, or it may be profuse enough to cause alarm in the mother or nurse. The bleeding usually occurs on the sixth or seventh day, but may appear later, rarely earlier. It is accompanied in many cases by an increased output of mucus, clear and fluid at first and later blood stained. This was not seen in Zacharias' cases. Often on the second day a small bloody fleck was noticeable at the vaginal outlet. It gradually became darker. The bleeding lasted one to three days. In no case was it accompanied by any signs of a general constitutional disturbance.

Von Zappert[26] recognized the uterus as the source of the blood. He found the muscular layer presented no special change, but that the blood vessels in the submucous tissue were overfilled and dilated, and in certain places he was able to demonstrate the actual escape of red blood corpuscles. The overlying epithelium was uninjured. There was no evidence of infection.

Halban[27] found that while the uteri of infants dying between the ages of 3 weeks and 2 years averaged 2.5 cm. in length, the uteri of eleven newly born infants averaged 3.2 cm. in length. Bayer (1902) had found that the uterus of newly born infants is larger than that of older infants, reaching sometimes ten times the volume found later in the first year. He found the following averages: seventh to ninth month of fetal life, 3 cm.; full-term newly born, 3.7 cm. (limits 4.2 and 4.5, Roderer). Halban found that the relatively large uterus of early infantile life gradually returns to normal size. This change is completed in about twenty-eight days after birth, and the process is termed by him "puerperal involution of the fetal uterus." Histologic study of the ovaries shows that they are entirely quiescent.

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27. Halban: Schwangerschaftsreaktion der fötal Organe und ihre puerperal Involution, Ztschr. f. Geburtsh., 1904, **53,** 191; Ueber fötale Menstruation und ihre Bedentung, Kongressbl. f. Gynekol., 1904, **28,** No. 2, p. 1270. Reference from Zacharias, Footnote 28.

28. Zacharias, Erich: Genitalblutung neugeborener Mädchen, Med. Klin., 1914, **10,** 1645.

Zappert viewed the whole process as a phenomenon of a physiologic rather than a pathologic nature. Halban extended this conception and advanced a new theory for the occurrence of genital bleeding in the newly born by suggesting that it was due to the action of some substance derived from the maternal placenta, circulating in the blood and acting as an internal secretion. The infantile uterus seems to become sensitive to such a substance in the eighth or ninth month of intrauterine life. This conception has found some experimental basis. Zacharias thinks that the mechanical factor of pressure on the abdominal organs during the birth of unusually large female infants may become a factor by predisposing the oversensitive uterus toward bleeding.

Clinically, the prognosis is always good, and the diagnosis alone is of interest. Inspection of the parts will usually reveal the source of the bleeding. Feer recommends the use of a small ear speculum. Congenital papillomatous growths of the vulva and vagina must be considered, also polyp-like prolapse of the urethral mucous membrane, with bleeding (Langstein), and congenital tumors with uterine bleeding. Much more common is sepsis with bleeding from the genital mucous membrane.

PATHOLOGY

During the past year there have appeared a considerable number of isolated reports of pathologic conditions in infants and children. A number of these will be referred to here. There have appeared also a few reports of a more extensive or monographic nature.

A paper of the latter type is a report by A. S. Warthin[29] of a study on the occurrence of malignant neoplasms in the young. Warthin's analysis tends to controvert the current statement that carcinoma is a disease of the old, and sarcoma of the young. It seems that the majority of these statements are derived from the writing of the Virchow period "when no exact differentiation of carcinoma and sarcoma was made, and when malignant teratoid tumors were classed as sarcoma or carcinoma, or chondroma, etc., as the case might be, according to the preponderance of one or the other of the elements making up the growth." The correctness of the diagnosis in many of the congenital and early life tumors is now in question, and so are, consequently, the generalizations based on them.

Warthin's material is a homogeneous one, derived almost entirely from the population of a single state, Michigan, and representing the average population of that state. The possibility of error in diagnosis

29. Warthin, A. S.: The Occurrence of Malignant Neoplasms in the Young as Shown by an Analysis of 2,000 Cases of Malignant Neoplasm Examined in the Pathological Laboratory of the University of Michigan, Arch. Int. Med., 1915, **15,** 444.

is reduced to a minimum by the material having been utilized both for purposes of practical diagnosis and for the teaching of pathologic histology.

In a total of 2,000 cases of neoplasm, Warthin found thus that 36 appeared before the age of 13 years (109 appeared in the next thirteen years). There were 33 cases of sarcoma, 2 cases of carcinoma, 1 in the fourth and 1 in the eleventh year; and 1 malignant teratoma. "The large number of cases in the first year emphasizes the importance of the congenital factor," says Warthin, and the influence is felt in the case of the majority of the tumors up to the period of sexual ripeness, even when no actual evidences of a teratoid nature could be demonstrated in the tumor. Sarcoma predominates in the period of infancy and childhood, but the parallel increase of both sarcoma and carcinoma with age (this is seen principally after the thirteenth year in the present series) is noteworthy, and in contradiction to the usual belief that sarcoma is essentially a disease of childhood.

Cases of malignant teratomas fall in the period of early childhood and developing sexual life, those of the testis and ovary, particularly, developing in the latter period.

Williams[30] pointed out the relative frequency of retinal gliomas and renal tumors in infancy and early childhood. No retinal gliomas appear in Warthin's series. Williams' work was based on Duzan's analysis of 182 malignant tumors of early infancy, Picot's analysis of 424 cases, his own of 56 consecutive cases. Poinset's 25 cases of bone sarcoma in infancy, Gross' study of sarcoma of the long bones (51 cases) and 41 cases tabulated by Butler and Colby. Warthin's conclusions agree in the main with those of Williams, and his view of the congenital or teratoid origin of malignant neoplasms in infancy and early life is supported. "Malignant tumors are relatively rare before puberty, but there is a steady ascending line of occurrence from childhood onward to middle life, both sarcoma and carcinoma showing a parallelism of occurence."

Hansell[31] has reported a case of bilateral glioma of the retina in a child of 2 years. He refers to Wintersteiner's classical monograph (467 cases) on nonpigmented cancer of the retina, and to the later studies of Wehrli, Lindenfeld, Fuchs, and others. Seventy-five to 80 per cent. of the cases occur in the first three years of life, and most within the first two years of life. About 24 per cent. of the cases are bilateral. Clinical histories emphatically negative the supposition that the other eye is involved sympathetically.

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30. Williams, W. R.: The Natural History of Cancer, New York, 1908.

31. Hansell, H. F.: A Case of Bilateral Glioma of the Retina, Am. Jour. Dis. Child., 1915, **11,** 485.

Williams[32] reports an instance of infiltration of the heart by large round-cell sarcoma in a boy of 8 years. Symptoms were of thirteen weeks' duration, pain in the left shoulder-joint, cough and much expectoration, with later vomiting, swelling of the eyelids and orthopnea. There were no enlarged veins.

Necropsy showed the anterior mediastinum filled with a hard white growth. This was adherent to the sternum, invaded the diaphragm, obliterated the pericardial space, enclosed the heart in a hard growth, and invaded the cardiac cavity. The mitral valve was thickened and appeared to be infiltrated. There were scattered growths in both pleurae. There was no enlargement of either the cervical or axillary glands. Microscopic examination showed the growth to be a large round-cell sarcoma, probably originating from the sternal periosteum.

Primary malignant growths of the pericardium are exceedingly rare; secondary growths arising in the mediastinum are scarcely more frequent. An instance is known in which the left ventricle was almost entirely invaded by the new growth.

ANOMALIES OF THE CARDIOVASCULAR SYSTEM

K. Secher[33] has described an instance of persistence of the primary paired longitudinal veins of the embryo. The condition was found at necropsy, in a 1½-year-old girl. There was aplasia of the left kidney, with hypertrophy of the right kidney and the left suprarenal gland. The external genitalia and the ovaries were symmetrically developed on the two sides, but the fallopian tube and the left horn of the uterus were smaller on the left than on the right side.

In place of one large vena cava inferior there were present two vessels which united to form one at a level just above that of the hilus of the persistent and hypertrophied right kidney. These two vessels Secher interpreted as persistent venae cardinales.

An instance of complete situs inversus is reported by Spallica.[34]

Moffett and Neuhof,[35] in a clinical report of congenital dextrocardia in a 3½-year-old boy, in whose case no necropsy was permitted, give a list of those cases of pure dextrocardia reported to date, 151 cases in all. The term "pure dextrocardia" is used here to signify those cases of dextrocardia in which the liver and spleen are normally placed. Moffett and Neuhof find no theory sufficiently convincing to

32. Williams, E. C.: Infiltration of the Heart by a Large Round-Celled Sarcoma, Brit. Jour. Child. Dis., 1916, **13,** 114.

33. Secher, K.: Ueber Aplasia renis Venae cardinalis persistentes, Berl. klin. Wchnschr., 1915, **52,** 487.

34. Spallica, A.: Su di un caso di situs viscerum inversus totalis, Riv. di Clin. Pediat., 1915, **13,** 185.

35. Moffett, R. D., and Neuhof, S.: Congenital Dextrocardia with Patent Interventricular Septum, Am. Jour. Dis. Child., 1915, **10,** 1.

explain all cases. The most prominent of the theories concerning the origin of pure dextrocardia is that in the prenatal development of the heart the right side develops more rapidly than the left and pulls the heart to that side.

Morse[36] reports a case of congenital anomaly of the heart in a 9-year-old boy. The child was first seen when 4 years old and was observed thereafter until his death. The picture was that of congenital heart disease, but no murmurs were detected, it is said, until a few months before his death, at which time subjective symptoms first developed.

The malformation with which it was thought the clinical symptoms were reasonably consistent were absence of the ventricular septum, transposition or irregular origin of the great vessels and pulmonary artery, with some secondary malformation. Postmortem examination of the heart revealed complete congenital atresia of the pulmonary artery, congenital defect of the interventricular septum, corresponding to the membranous portion, persistent ductus arteriosus, patent foramen ovale, dilatation and hypertrophy of the right ventricle, acute vegetative endocarditis, and thrombosis of the ductus arteriosus. Illustrative photographs accompany the report.

GASTRO-INTESTINAL TRACT

Chiari[37] has described an instance of infection of a congenitally syphilitic infant with hyphomycotic fungus. The infant died at 10 days of age, and at necropsy showed the usual evidences of congenital lues and a purulent peritonitis in the exudate of which probable colon bacilli were found. In addition to these lesions, there was present on the anterior wall of the stomach between the cardia and pylorus a circular, blackish discoloration of an area of about 5 square centimeters, with a yellowish center. The lesion extended through the thickness of the walls. On the inner surface there was a pea-sized loss of substance. The outer surface was bound to the liver by a fibrous exudate. Staining of the tissue, especially with carbolfuchsin, revealed numerous threads of a hyphomycete. Occasional masses of bacilli, apparently colon bacilli, were also seen. The threads of the fungus measured 6 to 10 microns in breadth.

Cases of similar infections, always of the stomach, have been described by Marchand (1910, 18-year-old girl); Benche (1911, 33-year-old man); Benilli (1912, 36-year-old woman), and Ljubimowa (1913, 64-year-old woman). The lesion appears as a small, sharply-

36. Morse, J. L.: A Case of Congenital Heart Disease with Demonstration of Specimen, Am. Jour. Dis. Child., 1915, **10,** 27.

37. Chiari, H.: Hyphomycosis ventriculi, Wien. med. Wchnschr., 1915, **65,** No. 1, p. 282.

defined area that in its dark gray color stands out sharply against the background. Where such areas are found, hyphomycotic infection should be thought of and examination for fungi should be made through cultural and staining methods.

A number of cases of congenital and other abnormalities of the gastro-intestinal tract have been reported.

Strauch[38] has described an instance of mesenterium commune with abnormal course of the jejunum found in dissecting the body of a 1-year-old boy. The condition was evidently a pure congenital anomally.

On opening the abdomen, loops of small intestine presented themselves, entirely covering the colon ascendens and transversum, with the exception of the hepatic flexure. On raising these loops of small intestine the cecum with the appendix was found in the region of the lower pole of the left kidney where they were completely and freely mobile. The colon ascendens passed from here upward to the hepatic region and was entirely free and mobile and without any fixation to the posterior abdominal wall, and had a long mesentery in common with the ileum and colon transversum.

The duodenojejunal flexure was not at its normal site nor in its proximity, but lay in a more dorsal plane behind the plate of the mesocolon commune, whence the jejunum emerged in an abnormal fossa and ran downward along the vertebral column. The sigmoid flexure was elongated, and even considering the age possessed a wide range of mobility. The course of the arteria mesenterica superior was abnormal.

The condition finds its explanation in disturbance of the normal rotation of the originally free umbilical loop and the normal coalescence of the mesenteries and the intestinal segments with the posterior abdominal wall. Instances of failure of rotation have been reported by Mayo[39] and others; while rotation of the primitive umbilical loop in the reversed direction results in situs inversus intestini, which may be more or less incomplete. The occurrence of such conditions is of interest from the standpoint of embryology, teratology and operative surgery. Boyd[40] has recently considered this in relation to appendectomy and the performance of gastroduodenostomy.

Holmes[41] has reported an instance of congenital obliteration (atresia) of the extrahepatic bile ducts. The child, a 7-weeks-old boy, presented the usual clinical picture, and died at 15 weeks of age. The

38. Strauch, August: Mesenterium Commune with Abnormal Course of Jejunum, Am. Jour. Dis. Child., 1916, **11,** 208.

39. Mayo, C. H.: Med. Rec., New York, 1912, **81,** 401.

40. Boyd, S.: Brit. Med. Jour., 1914, **2,** 507.

41. Holmes, J. B.: Congenital Obliteration of the Bile Ducts; Diagnosis and Suggestions for Treatment, Am. Jour. Dis. Child., 1916, **11,** 405.

gallbladder was atrophic, the arrangement of the hepatic ducts was anomalous, in that they opened independently into a small globular chamber; the cystic and common ducts were obliterated through the greater part of their course. The pancreas, its ducts, and the duodenal papilla were normal. There were no evidences of any inflammatory origin, and the condition seems most readily explained as an anomaly of development.

Holmes reviews the literature of the subject and presents diagrams showing the nature and extent of the lesions in the 120 odd cases reported to date. It appears that diagnosis can usually be made and that operative relief is anatomically possible in at least 16 per cent. of all cases. The technical difficulties have already been in great part overcome.

Drennan and Clark[42] report a case of multiple complete congenital obstruction of the intestine in an infant. Aside from imperforate anus, congenital obstructions of the intestine are infrequent. The small intestine is more often involved than the large intestine. According to Leichenstein,[43] the proportion of congenital malformations of the intestine is as follows: 375 at the anorectal junction, 75 in the small intestine and 10 in the colon. In the small intestine, atresia is more often seen than stenosis. The common site is in the duodenum. Usually but one point of actual obstruction is found; beyond these one or more points of stenosis are sometimes found. Few if any cases of complete multiple congenital obstructions of the jejunum have been previously reported.

Drennan and Clark's case was a 4-day-old white boy. He began to vomit as soon as he was put to the breast. This was repeated after every feeding. The vomited matter was bile-stained mucus and milk. Enemas were unproductive. Laparotomy revealed a high congenital malformation of the intestine and also points of stenosis. Necropsy revealed four complete congenital occlusions of the small intestines. "The first one was 28 cm. from the pyloric ring, and the form of occlusion was that of a thin tissue diaphragm lined on its upper surface by the usual type of mucous membrane, while below it had a smooth parchment-like surface. The duodenum and the portion of the jejunum above this partition had been a large food reservoir for all the food taken, and therefore was tremendously dilated and the wall thickened." The second obstruction was found 15 cm. below this, the bowel simply tapered off to a solid cord of tissue, 3 to 4 cm. in length and 1 mm. in

42. Drennan, L. M., and Clark, H. C.: A Congenital Malformation of the Intestine; Multiple Points of Complete Obstruction, Am. Jour. Dis. Child., 1915, **10,** 360.

43. Leichenstein, in Osler's Modern Medicine: Lea & Febiger, Philadelphia and New York, 1908, **5,** 458.

thickness; the lumen above contained only clear mucous fluid. A third obstruction, 10 cm. below this, was similar in nature. The fourth obstruction occurred 42 cm. below the third and was a membranous partition like the first one. A small persistent foramen ovale was the only other congenital malformation found in the body.

W. P. Erus[44] reports a case of congenital infrapapillar atresia of the duodenum that was corrected surgically by anastomosis.

O. Sachs[45] reports a case of dilatation of the large bowel, simulating Hirschsprung's disease, that occurred in a 7-year-old boy who had suffered from constipation from birth. Examination showed an anal aperture of small diameter, ¼ cm., and fibrous margin. At operation this was found to admit to a fibrous passage about 4 cm. long, which led to a much dilated rectum filled with stony, hard fecal masses. A plastic operation brought temporary relief and further surgical treatment completed the cure. The symptoms of Hirschsprung's disease disappeared entirely and the abnormality of the large intestine was clearly the result of anal stenosis alone.

Sachs calls attention to other analogous cases in the literature; for example, a month-old infant in whom a small congenital angiomatous tumor and a fissure led to dilatation and hypertrophy of the colon; another in which a smooth, circular, subcutaneous congenital fibrous band led to anal stenosis, and secondarily to dilatation of the colon; and also one in which the use of ordinary soap as a suppository led to severe irritation of the anus and rectum, fibrous stenosis, and secondary changes above.

An instance of congenital atresia of the colon is mentioned by Rivarola.[46] No details are given.

Conciliis[47] reports a case of multilocular lymphatic cysts of the mesocolon in a 9-year-old boy. Symptoms had appeared fifteen days before. The child had been seized with violent abdominal pain, and a tumor became evident in the epigastrium and left hypochondrium. Previously he had been well; thereafter purges were required. An incarcerated umbilical hernia was thought of. Operation revealed multiple cysts of the mesocolon, ranging downward from the size of an orange. According to Conciliis, these tumors would be considered multilocular lymphatic cysts by the clinician. The pathologist would regard them, histologically, as cystic or cystoid lymphangiomas (Wegener). Such cysts of the mesocolon are not common. Deaver, in 1909, was able to collect only 134 cases from the literature.

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44. Erus, W. P.: Hospitalstid., Oct. 27, 1915.

45. Sachs, Otto: Ein Fall Einer Analstenose, einen echten Hirschsprung's vortauschend, Jahrb. f. Kinderh., 1915, **81,** 469.

46. Rivarola: Societa Argentina di Pediatria, La Pediatria, 1915, **23,** 618.

47. De Conciliis, Ugo: Cisti linfatica mulilocolare del mesocolon in un bambino, La Pediatria, 1915, **23,** 643.

Bythell[48] reports an instance of hernia of the stomach through the esophageal opening in the diaphragm. The previous history consisted of attacks of persistent vomiting for about six months, the condition steadily getting worse. Apparently there was never at any time much abdominal pain. On exploration, the major part of the stomach was found to be herniated through the esophageal opening. The other abdominal organs were normal. The stomach was brought down and stitched to the anterior abdominal wall. It later escaped. At a second operation a gastrostomy was done.

Volpe[49] reports a case of congenital defect in the diaphragm which permitted the terminal portion of the duodenum, the small intestine, the cecum, appendix, and much of the colon to pass up into the left side of the thorax. The infant presented a normal appearance at birth, but remained cyanotic, and soon died. Volpe considers this anomally at some length and presents a full bibliography. Nau has classified such cases as (1) those in which the separation of the pleural and peritoneal spaces, originally one in early embryonic life, is never completed, and (2) those in which a defect in the musculature or fibrous tissue of the diaphragm permits a sacculated hernia upward. Volpe's case was of the first type.

Another case is reported by R. Monti.[50]

CENTRAL NERVOUS SYSTEM

Strauch[51] has reviewed the subject of pachymeningitis hemorrhagica interna in infants. Summarizing various theories and certain experimental work, he concludes that pachymeningitis hemorrhagica interna as it occurs in infancy is most probably an infectious disease, caused by the meningococcus or other organisms. The meningococcus and other organisms may produce now leptomeningitis, now pachymeningitis; the two processes may be more or less combined in certain cases. The early observations of Weichselbaum[52] would tend to confirm this view, as would also recent studies of Rosenow.[53]

His own case was a purely clinical one, no necropsy being granted. Lumbar puncture at different times yielded a large gram-negative coccus that was characteristically agglutinated by serums containing

48. Bythell, W. S. G.: Hernia of the Stomach Through the Diaphragm in a Child Aged 9 Years, Brit. Jour. Child. Dis., 1915, **12,** 236.

49. Volpe, Carlo: A Proposito di un caso di erniä diaprammatica congenita in un neonato, Riforma med., 1915, **31,** 1125.

50. Monti, R.: Wien. klin. Wchnschr., 1915, **31,** 1125.

51. Strauch, A. B.: Am. Jour. Dis. Child., 1916, **11,** 23.

52. Weichselbaum, A.: Ueber die Aetologie des akuten Meningitis cerebrospinale, Fortschr. d. Med., 1887, **5,** 620.

53. Rosenow, E. C.: Jour. Infect. Dis., 1915, **16,** 240; ibid., **16,** 367; ibid., **17,** 219.

specific agglutinins (serum from a patient convalescent from epidemic meningitis, and antimeningitis serum in dilution of 1:60 to 1:80).

Holmes[54] has reported a case of large multiple cerebral abscesses in an infant of 23 months. The child developed symptoms of hydrocephalus at 18 months of age, and the condition progressed to death under the picture of chronic internal hydrocephalus of the obstructive type. After death two large and three smaller abscesses were found occupying the posterior half of the left cerebral hemisphere. They were apparently of pyogenic origin. But the presence of organisms could not be demonstrated. Neither the history nor the necropsy findings suggested a portal of entry. The tissue was noteworthy in the large size of the abscess cavities (6.2 by 5 by 7.5 cm.), in the unusual development of pyogenic membranes, and in the presence of numerous and well-defined examples of the so-called cerebral granule cells, or Gluge's corpuscles.

Certain phases of the literature on the subject are reviewed by Holmes. Cases of cerebral abscess occurring in infants so young as his patient appear to be exceedingly rare (Okada, Heiman). Recent experimental work (Tanaka and others) indicates that cerebral granule cells are derived from preexisting glia cells.

Smith[55] reports an instance of acute myelitis appearing two weeks after the onset of varicella, with very widespread eruption, in a 7-year-old boy. The child's recovery was still incomplete a year later.

Acute myelitis is not altogether an uncommon accompaniment of infectious diseases such as typhoid fever, malaria, scarlatina, variola, acute rheumatism, measles, dysentery, gonorrhea, pneumonia, and streptococcus and staphylococcus infection. Councilman has mentioned varicella as a cause. In Smith's case symptoms of myelitis followed so closely an infection with varicella as to justify the assumption of a definite etiologic relationship.

GENITO-URINARY SYSTEM

Losee[56] reports three cases of congenital anomaly of the kidney, one congenital hydronephrosis, one typical horseshoe kidney, and a unilateral fused kidney. The specimens were obtained from stillbirths.

The first was the size of a grapefruit and was divisible into two parts, a lobulated thinned-out cortex without any microscopic evidence of normal renal tissue, and a lower portion with a smooth, firm wall

54. Holmes, J. B.: Multiple Abscesses of the Brain in Infancy, Arch. Int. Med., 1916, **17,** 591.

55. Smith, D. C. W.: Acute Myelitis Following Varicella. Am. Jour. Dis. Child., 1915, **10,** 445.

56. Losee, J. R.: Report of Three Cases of Congenital Anomaly of the Kidney, Bull. Lying-In Hosp., 1915, **10,** 101.

continuous with the ureter. There was a stricture in the ureter at the point where it joined the pelvis, and it varied in size throughout the remainder of its course. The cyst contained a pale, straw-colored fluid in which there was no urea present. The right kidney presented two small cysts of the cortex; its ureter entered the hilum in the normal manner.

Of twenty cases collected by Roberts, thirteen were bilateral. An imperforate urethra is the usual cause of these. The most common cause of unilateral congenital hydronephrosis is stricture of the ureter at its junction with the pelvis. Stricture of the ureter at its vesical extremity, kinking of the ureter, and compression of it by a supernumerary artery (Roberts), are other causes.

In horseshoe kidney the fusion is more common at the lower poles. It takes place in the fifth to seventh week of embryonic life, when the kidney is a pelvic organ. Fusion of the upper poles generally takes place after the kidney has migrated upward. The pelves are then well developed independent structures and do not fuse. According to the structure, fusion of the kidneys may be of three grades: (1) the lower poles are united by a fibrous band; (2) the bridge consists of only the cortex of the kidney, and (3) the bridge is broad and thick and consists of all the structures of a normal kidney. The anomaly occurs in 0.08 per cent. of necropsies (Morris and Socin, 16,000 necropsies).

In Losee's specimen of horseshoe kidney, the organs were united by their lower poles. The pelves of the two sides were not continuous, though that on the right side was divided into the communicating portions. Two ureters arose from the pelvis of the right kidney, one from the upper portion and one from the bridge. They ran a parallel course and united in a common orifice in the trigon. The one ureter from the left kidney took the usual course.

The specimen of sigmoid kidney, or unilateral fused kidney, represents a rarer anomaly. The kidney was diagonally located, the upper pole lying on the left side of the abdomen opposite the first lumbar vertebra, and the lower pole in the bony pelvis. The pelves were not continuous. The ureters were single, normal in size, and entered the bladder normally. That on the right entered a small hilum on the anterior surface of the inferior portion of the kidney; that on the left entered another hilum near the superior pole.

The position of the kidney and the fact that two ureters enter the bladder on different sides distinguishes the case from one of complete absence of one kidney. In the last mentioned anomaly one of the kidneys either fails to bud off from the Wolffian duct, or passes through the first stage and becomes arrested and later absorbed.

Rolleston[57] reports an instance of a single pelvic kidney, in a

57. Rolleston, J. D.: Single Pelvic Kidney, Brit. Jour. Child. Dis., 1916, **13,** 80.

14-year-old boy, situated on the right side within the brim of the pelvis, and lying in apposition to the posterior wall of the bladder. It was irregular in shape and reniform, and was lobulated. It measured 3¼ inches in length, and 1 inch in thickness, and varied in width from 1¾ inches at its upper part, to 2⅛ inches at its lower part, and weighed 4 ounces. The hilus was situated arteriorly, and from it issued a single ureter which was evidently dilated and hypertrophied, but at its vesical extremity barely admitted a pin's head. There was some dilatation of the pelvis and calices of the kidney, but no marked degree of hydronephrosis. No trace of a left kidney or ureter could be found. There was no malformation of the genital organs. The boy died of septic scarlet fever. He was mentally defective.

Rolleston gives much interesting historical and clinical data in his report. Single or a symmetrical kidney (renal aplasia or agenesis) is extremely uncommon, being found in only one out of 2,400 necropsies (Morris). About 300 cases, some of them doubtful, are on record. Congenital displacement of the kidney, or renal distopia, is less uncommon. Its frequency is estimated at one in five hundred (Girard) to one in one thousand (Guizetti and Pariset).

Kakels[58] reports an instance in which a large congenital hydronephrosis in an infant of 6 weeks was diagnosed with considerable certainty by the history, physical signs and Roentgen-ray findings, and successfully removed by transperitoneal nephrectomy. The child made an uneventful recovery. The sac contained nearly a liter of straw-colored fluid. The ureter was found perfectly normal throughout its whole length, with no dilatation or stricture. Its insertion into the sac was at some distance from the blood vessels, and it lay flat on the surface of the sac. Its obliquity of entrance and its anomalous position may have been an etiologic factor in the cause of the hydronephrosis.

Another case of congenital hydronephrosis is reported by Williams.[59] It occurred in a male infant of 6 months. Clinically there was marked intestinal peristalsis. The ureters could be felt on either side and the right one resembled an intussusception. There was almost complete suppression of urine. Necropsy showed both ureters the size of the small intestine and the bladder much hypertrophied. There was no demonstrable fold in the urethra to cause obstruction.

LYMPHATIC SYSTEM

Schridde[60] has considered the possibility of status thymolymphaticus being in some instances a congenital condition. He has made post-

58. Kakels, M. S.: Large Congenital Hydronephrosis in an Infant 6 Weeks of Age, New York Med. Jour., 1916, **103,** 547.

59. Williams, E. C.: Brit. Jour. Child. Dis., 1916, **13,** 50.

60. Schridde, Hermann: Der Angeborene Status Thymolymphaticus, München. med. Wchnschr., 1914, **61,** 2161.

mortem examinations of fifty-nine still-born infants, and finds that in fetal material, even up to full-term birth, the lymph nodes in the spleen and intestine are not visible. The tonsils are visible, but it is difficult to draw conclusions as to their size.

He finds the thymus presents the following normal range of variation in weight: fetuses, 42 cm. long, 3 to 11 gm.; 46 cm. long, 8 to 14 gm., and 47 cm. long, 4 to 11 gm. The weight of the spleen ranges up to 15 gm. in fetuses of 48 cm. length; and at 51 cm. length, from 22 to 27 gm. The range of normal variation is so great that the weight of these organs, the thymus and spleen, may not safely be used as an index.

Among the fifty-nine fetuses examined, Schridde found three in which the thymus seemed to him abnormally large. At 54 to 55 cm. fetal length, the thymus weighed 19, 24 and 26 gm., respectively. There was marked hyperplasia of the lymphoid tissue, and the lymph-nodes in the spleen and intestines were visible.

Wernstedt[61] thinks that in nurslings, at least, thymuses of 20 to 30 gm. weight are to be regarded as normal. In fourteen infants who died suddenly in good nutritional condition, the thymus weighed 21.6 to 57.1 gm.

LIPODYSTROPHIA PROGRESSIVA

Feer[62] reports two cases of this little known condition. It is characterized by the occurrence of more or less symmetrically distributed and progressive atrophy of the subcutaneous fat of the patient. Earlier reports on the subject are those of A. Simons[63] and Husler.[64]

Feer's patients were 9½- and 10-year-old girls. His report is accompanied by a study, by one of his pupils,[65] of the normal thickness of the subcutaneous tissue in healthy and ill children.

The Severn.

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61. Wernstedt, W.: Die Infantile Larynstridor (Stridor congenitus), Nord. Med. Arch., a. f. d. 11, Parts 1 to 4, No. 22; Abstr. in Monatschr. f. Kinderh. (Referate), 1915, **14,** 397.

62. Feer: Lipodystrophia progressiva, Jahrb. f. Kinderh., 1915, **82,** 1.

63. Simons, A.: Eine seltene Trophoneurose (Lipodystrophia progressiva), Ztschr. f. d. ges. Neurol u. Psychol., Orig., 5, 1911, **19,** 1913.

64. Husler, J.: Ueber symmetrischen progressiven Fettschwund im Kindesalter, Ztschr. f. Kinderh., 1914, **10.**

65. Batkin, S.: Die Dicke des Fettpolsters bei gesunden und kranken Kindern, Jahrb. f. Kinderh., 1915, **28,** 103.

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ERRATA

In the article by Dr. Alfred F. Hess on "Infantile Scurvy" in the January number, page 99, line 9, the specific gravity should be 1.4 instead of 1.04. Page 109, line 15, read "16 ounces," not "sixteen months."